DOCKET

SUPREME COURT
OF THE UNITED STATES

No. 10-844
Title: Caraco Pharmaceutical Laboratories, Ltd., et al., Petitioners
v
Novo Nordisk A/S, et al.
Docketed: December 28, 2010
Linked with 10A380
Lower Ct: United States Court of Appeals for the Federal Circuit
Case Nos.: (2010-1001)
Decision Date: April 14, 2010
Rehearing Denied: July 29, 2010
Questions Presented:

~~Date~~~	~~~~~~~~Proceedings and Orders~~~~~~~~~~~~~~~~~~~~~~
Oct 15 2010	Application (10A380) to extend the time to file a petition for a writ of certiorari from October 27, 2010 to December 26, 2010, submitted to The Chief Justice.
Oct 18 2010	Application (10A380) granted by The Chief Justice extending the time to file until December 23, 2010.
Dec 23 2010	Petition for a writ of certiorari filed. (Response due January 27, 2011)
Jan 10 2011	Order extending time to file response to petition to and including February 25, 2011.
Jan 27 2011	Brief amicus curiae of Teva Pharmaceuticals USA, Inc. filed.
Jan 27 2011	Brief amicus curiae of Generic Pharmaceutical Association filed.
Jan 27 2011	Brief amici curiae of Consumer Federation of America and U.S. PIRG filed.
Jan 27 2011	Brief amicus curiae of Mylan Pharmaceuticals, Inc. filed.
Jan 27 2011	Brief amicus curiae of Apotex, Inc. filed.
Feb 25 2011	Brief of respondents Novo Nordisk A/S, and Novo Nordisk Inc. in opposition filed.
Mar 7 2011	Reply of petitioners Caraco Pharmaceutical Laboratories, Ltd., et al. filed.
Mar 9 2011	DISTRIBUTED for Conference of March 25, 2011.
Mar 28 2011	The Acting Solicitor General is invited to file a brief in this case expressing the views of the United States.
May 26 2011	Brief amicus curiae of United States filed.
Jun 3 2011	Supplemental brief of respondents Novo Nordisk A/S, and Novo Nordisk Inc. filed.
Jun 7 2011	DISTRIBUTED for Conference of June 23, 2011.
Jun 7 2011	Supplemental brief of petitioners Caraco Pharmaceutical Laboratories, Ltd., et al. filed. (Distributed)
Jun 27 2011	Petition GRANTED.
Jul 13 2011	The time to file the joint appendix and petitioners' brief on the merits is extended to and

	including August 29, 2011.
Jul 13 2011	The time to file respondents' brief on the merits is extended to and including October 17, 2011.
Aug 16 2011	Consent to the filing of amicus curiae briefs, in support of either party or of neither party, received from counsel for the respondents.
Aug 29 2011	Joint appendix filed (two volumes). (Statement of costs filed)
Aug 29 2011	Brief of petitioners Caraco Pharmaceutical Laboratories, Ltd., et al. filed.
Sep 6 2011	Brief amicus curiae of United States filed.
Sep 6 2011	Brief amicus curiae of Generic Pharmaceutical Association filed.
Sep 6 2011	Brief amicus curiae of Rep. Henry A. Waxman filed.
Sep 6 2011	Brief amici curiae of AARP and U.S. PIRG filed.
Sep 6 2011	Brief amicus curiae of Mylan Pharmaceuticals, Inc. filed.
Sep 12 2011	SET FOR ARGUMENT ON Monday, December 5, 2011.
Sep 19 2011	CIRCULATED
Sep 26 2011	Record received from U.S.C.A. for Federal Circuit. (1 box)
Sep 27 2011	Motion of the Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument filed.
Oct 17 2011	Brief of respondents Novo Nordisk A/S, and Novo Nordisk Inc. filed. (Distributed)
Oct 24 2011	Brief amici curiae of Allergan, Inc., et al. filed. (Distributed)
Oct 24 2011	Brief amicus curiae of Pharmaceutical Research and Manufacturers of America filed. (Distributed)
Oct 24 2011	Brief amicus curiae of Washington Legal Foundation filed. (Distributed)
Nov 7 2011	Motion of the Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument GRANTED.
Nov 16 2011	Reply of petitioners Caraco Pharmaceutical Laboratories, Ltd., et al. filed. (Distributed)
Dec 5 2011	Argued. For petitioners: James F. Hurst, Chicago, Ill., and Benjamin J. Horwich, Assistant to the Solicitor General, Department of Justice, Washington, D. C. (for United States, as amicus curiae.) For respondents: Mark A. Perry, Washington, D. C.

PETITION FOR WRIT OF CERTIORARI

No. ____

In the Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD. AND SUN PHARMACEUTICAL INDUSTRIES, LTD., PETITIONERS

v.

NOVO NORDISK A/S AND NOVO NORDISK, INC., RESPONDENTS

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

When the Food & Drug Administration (FDA) approves a drug for multiple uses, the Hatch-Waxman Act allows generic drug makers to avoid contested patent litigation by marketing generic versions of the drug solely for non-patented uses. The FDA lacks the authority and expertise needed to verify the patent information submitted by name-brand drug companies, however, so it defers to their descriptions of the scope of their patents. Such companies can therefore block the approval of generic drugs by submitting overbroad patent descriptions to the FDA, effectively extending their patents to cover non-infringing uses.

To combat this problem, the Act allows a "counterclaim seeking an order requiring the [patent] holder to correct or delete the patent information submitted by the holder * * * on the ground that the patent does not claim * * * an approved method of using the drug." 21 U.S.C. § 355(j)(5)(C)(ii)(I). In a 2-1 decision that conflicts with this Court's precedents and recent D.C. Circuit authority, the Federal Circuit held that the counterclaim provision effectively authorizes only "delet[ing]" improperly listed patents, but not "correct[ing]" information that misrepresents the scope of the approved uses claimed by a patent. That ruling expressly invalidates longstanding FDA regulations defining "patent information," which the FDA deems "essential" to administering the Act, without seeking the agency's views. The question presented is:

> Whether this counterclaim provision applies where (1) there is "an approved method of using the drug" that "the patent does not claim," and (2) the brand submits "patent information" to the FDA that misstates the patent's scope, requiring "correct[ion]."

PARTIES TO THE PROCEEDINGS

Petitioners are Caraco Pharmaceutical Laboratories, Ltd., a publicly traded company, and Sun Pharmaceutical Industries, Ltd., a publicly traded company that owns a majority of Caraco's shares. Sun has no parent corporation.

Respondents are Novo Nordisk A/S and Novo Nordisk, Inc. Upon information and belief, Novo A/S owns more than 10 percent of the stock of Novo Nordisk A/S and Novo A/S, in turn, is fully owned by the Novo Nordisk Foundation.

The amici curiae in support of rehearing or rehearing en banc below were the Generic Pharmaceutical Association; Apotex, Inc.; the Consumer Federation of America; the National Legislative Association on Prescription Drug Prices; Mylan Pharmaceuticals Inc.; and Teva Pharmaceuticals USA, Inc.

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GLOSSARY OF ABBREVIATIONS

Act	Hatch-Waxman Act
ANDA	Abbreviated New Drug Application
Counterclaim	21 U.S.C. § 355(j)(5)(C)(ii)(I)
FDA	Food & Drug Administration
NDA	New Drug Application
Orange Book	FDA Orange Book Approved Products With Therapeutic Equivalence Evaluations
Paragraph IV	21 U.S.C. § 355(j)(2)(A)(vii)(IV)
Section viii	21 U.S.C. § 355(j)(2)(A)(viii)

INTRODUCTION

Petitioners ("Caraco") seek review of a splintered Federal Circuit decision raising issues of recurring importance under the Hatch-Waxman Act.[1] This ruling enables name-brand manufacturers to use their patents to block generic manufacturers from marketing drugs that *concededly* do not infringe.

The question presented is vitally important to the $300 billion pharmaceutical industry and the FDA, which administers the statute. In conflict with this Court's precedents and recent D.C. Circuit authority, the decision below effectively nullifies both a critical provision of the Act and related FDA regulations—which Congress ratified in 2003—without calling for the FDA's views. Each panel member, and the dissent from the denial of en banc review, recognized that the decision "tip[s] the [Act's] careful balance in the favor of pioneering manufacturers." Pet. 14a (Rader, J.); Pet. 20a-21a (Clevenger, J., concurring); Pet. 40a (Dyk, J., dissenting); Pet. 59a (Gajarsa and Dyk, JJ., dissenting from denial of rehearing). This extraordinary result compels review, particularly under a law designed to *expedite* generic competition.

Here is the problem. When a drug has multiple FDA-approved uses and a patent claims at least one, but not all, of those approved uses, "Section viii" of the statute allows generics to obtain FDA approval to market the drug with a "carve-out label" that omits

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[1] The "Hatch-Waxman Act" refers to the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984), as amended by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003).

reference to infringing uses. Pet. 6a. Caraco seeks FDA approval to market generic repaglinide—a diabetes drug manufactured by respondents ("Novo")—for two uses that Novo *concedes* do not infringe its patent. Every panel member agreed that Caraco qualifies for a Section viii carve-out label.

Over a forceful dissent, however, the Federal Circuit held that Novo could block approval of Caraco's product by deliberately providing the FDA with a description of its patent erroneously indicating that it *does* cover Caraco's proposed uses. Shortly after the FDA rejected Novo's challenge to Caraco's carve-out label, Novo submitted a newly broadened description of its patent to the agency. As the district court held, Novo's new description "seriously misrepresents" the patent's scope. Pet. 70a. But the FDA—which lacks the requisite legal authority and expertise to substantively review patents—defers to the brand's patent description, known as a "use code." Novo's newly minted use code thus caused the FDA to reverse itself and reject Caraco's carve-out label—thereby barring Caraco from marketing its drug for uses that everyone agrees are non-infringing.

The question presented boils down to whether the Act remedies such gamesmanship. It does. It authorizes counterclaims to "correct or delete the patent information submitted by the [patent] holder" whenever there is "an approved method of using the drug" that "the patent does not claim," and the brand's "patent information" is inaccurate, requiring "correct[ion]." 21 U.S.C. § 355(j)(5)(C)(ii)(I).

Yet contrary to the Act's text, structure, legislative history, and interpretation by the FDA, a divided Federal Circuit panel held that Caraco has no rem-

edy. By the majority's lights, no counterclaim is available because (1) Novo's patent claims *one* approved use, even though it "does not claim" two *other* "approved method[s] of use"; and (2) the counterclaim is effectively limited to "delet[ing]" wrongly-listed patents, when Congress also authorized "correct[ing]" patent information. Pet. 12a. The majority reached this result by announcing that the phrase "an approved method of us[e]" *really* means "*any* approved method of us[e]." *Ibid.* But that rewriting of the Act violated this Court's precedents—not least because the word "any" appears elsewhere in the same provision. Moreover, the majority read the term "patent information" as limited to "an erroneous patent number or expiration date"—*i.e.*, to exclude "use codes"—invalidating the FDA's contrary interpretation, which Congress ratified. Pet. 16a.

Accordingly, brands may now craft highly generalized use codes (*e.g.*, "a method for treating diabetes"), which "effectively allows [them] to extend [their] monopol[ies] to unpatented uses." Pet. 62a (Gajarsa, J., dissenting). In other words, brands can "insulat[e] themselves from generic competition and render[] Section viii"—"a critical provision" that "facilitates the approval and marketing of lower-cost generic drugs for uses no longer protected by a patent"—"a dead letter." Pet. 62a, 59a. Not surprisingly, the FDA's counsel has publicly stated that, since the ruling below, a solution to the problem of overbroad use codes has eluded the agency.

If Hatch-Waxman is to be read as leaving generics without any remedy to address this manipulation of FDA approval, that result should come from a decision of this Court—not from a dubious Federal Circuit ruling that split three ways, conflicts with this

Court's precedents and D.C. Circuit authority, and threatens the FDA's administration of the Act. The petition should therefore be granted.

OPINIONS BELOW

The Federal Circuit's opinion (Pet. 1a-52a) is reported at 601 F.3d 1359. The Federal Circuit's decision denying rehearing and rehearing en banc (Pet. 53a-64a) is reported at 615 F.3d 1374. The relevant decisions of the District Court for the Eastern District of Michigan (Cohn, J.) (Pet. 65a-103a) are reported at 649 F.Supp.2d 661 and 656 F.Supp.2d 729.

JURISDICTION

The Federal Circuit entered judgment on April 14, 2010, and denied a timely rehearing petition on July 29, 2010. On October 18, 2010, the Chief Justice extended the time to petition for certiorari to December 23, 2010. This Court has jurisdiction under 28 U.S.C. § 1254(1).

STATUORY AND REGULATORY PROVISIONS INVOLVED

Relevant statutory and regulatory provisions are set forth at Pet. 104a-210a.

STATEMENT

A. The structure of the Hatch-Waxman Act

The Hatch-Waxman Act governs FDA approval of new and generic drugs. 21 U.S.C. § 355. The Act is designed to "strike a balance between two competing policy interests: (1) inducing pioneering research and development of new drugs and (2) enabling competitors to bring low-cost, generic copies of those drugs to market." *Caraco Pharm. Labs, Ltd.* v. *Forest Labs., Inc.*, 527 F.3d 1278, 1282 (Fed. Cir. 2008) (citations

and brackets omitted), cert. denied, 129 S. Ct. 1316 (2009). Because new drugs are often protected by patents, the Act stands at the intersection of patent law and the FDA drug approval process.

Notwithstanding the Act's importance, this Court has addressed its application just twice. See *Merck KGaA* v. *Integra Lifesciences I, Ltd.*, 545 U.S. 193 (2005); *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661 (1990). Moreover, the Court has never addressed the Act's provisions governing approval of generic marketing, at issue in hundreds of cases annually.

As detailed below, the Act provides different ways for generic manufacturers to obtain FDA approval to market generic drugs. Most relevant here are the "Paragraph IV" process, which facilitates resolution of patent infringement disputes between name-brand and generic companies; and the "Section viii" process, which avoids such litigation and speeds market entry when generics seek to sell drugs for uses *not* covered by any patent. In both instances, "Congress sought to get generic drugs into the hands of patients at reasonable prices—fast." *In re Barr Labs., Inc.*, 930 F.2d 72, 76 (D.C. Cir. 1991).

1. Abbreviated New Drug Applications

To expedite FDA approval, the Act allows generic manufacturers to submit to the FDA an abbreviated new drug application (ANDA) instead of a full-blown new drug application (NDA). 21 U.S.C. § 355(j)(2)(A). An ANDA may rely on safety and efficacy studies previously submitted by brands. The timing of an ANDA's approval, however, depends largely on the scope of the patents covering the name-brand drug and, if necessary, resolution of litigation over patent infringement. Accordingly, NDA filings must identify

all non-process patents that arguably protect the new drug. *Id.* § 355(b)(1), (c)(2). The FDA lists these patents in its book of "Approved Products With Therapeutic Equivalence Evaluations"—the "Orange Book"—which alerts generics to the scope of claimed patent rights. Pet. 4a-5a.

a. Paragraph IV applications

As relevant here, the Act provides two distinct means of obtaining FDA approval of an ANDA. If a generic manufacturer seeks to market a drug arguably covered by an unexpired patent listed in the Orange Book, "the generic is generally required to certify that the patent * * * is invalid or will not be infringed by the sale or use of the [generic] drug." Pet. 24a. This is called a "Paragraph IV" certification. 21 U.S.C. § 355(j)(2)(A)(vii)(IV).[2]

The Act treats a Paragraph IV certification as an artificial act of patent infringement, permitting the brand to sue the generic. 35 U.S.C. § 271(e)(2).[3] If the generic wins and its ANDA otherwise qualifies, the FDA must approve the ANDA on the "date" when the district court enters judgment. 21 U.S.C. § 355(j)(5)(B)(iii)(I). And if the generic is the first to file a Paragraph IV certification for that drug (a "first

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[2] Alternatively, a generic may certify that: (I) the required patent-related information has not been filed; (II) the patent has expired; or (III) the patent will soon expire. *Id.* § 355(j)(2)(A)(vii)(I-III).

[3] If the NDA holder does not sue within 45 days, the FDA may approve the ANDA; if the NDA holder sues, approval is automatically stayed for 30 months or until a court holds each listed patent not infringed or invalid, whichever comes first. 21 U.S.C. § 355(j)(5)(B)(iii).

filer"), it receives 180 days of market exclusivity. *Id.* § 355(j)(5)(B)(iv).

b. Section viii applications

The Act also offers an alternative means of obtaining approval of an ANDA—a "Section viii" statement. "Section viii addresses scenarios where a patent claims at least one, but not all, approved methods of using a drug." Pet. 13a-14a. Section viii applies when the patent on a chemical compound used in a drug has expired, and the Orange Book lists a "method" patent—one covering a specific method of using the compound—that "does not claim a use for which the applicant is seeking approval." 21 U.S.C. § 355(j)(2)(A)(viii); *Purepac Pharm. Co.* v. *Thompson*, 354 F.3d 877, 880 (D.C. Cir. 2004).

Section viii allows a generic to "submit a proposed label to the FDA that does not contain [*i.e.*, carves out] the patented method of using the listed drug." Pet. 5a.[4] By obtaining approval to "delet[e] patented use[s] from its proposed label," generics "avoid infringement." Pet. 60a.

Importantly, however, the FDA lacks both institutional "expertise in patent matters" and a "statutory basis" to interpret patents. *Applications for FDA Approval to Market a New Drug*, 68 Fed. Reg. 36676, 36682 (June 18, 2003). Thus, "[the FDA's] role in listing patents in the Orange Book is 'ministerial'; it simply lists the patent information that it receives from brand manufacturers, expecting those parties to

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[4] Normally, the generic's label must be identical to the brand's. 21 U.S.C. § 355(j)(2)(A)(v), (j)(4)(G); 21 C.F.R. § 314.94(a)(8)(iv).

properly abide by the statutory and regulatory mandates." Pet. 60a-61a n.4.

This brand-authored patent information is known as a "use code narrative," or simply a "use code." Pet. 4a. "The FDA approves the section viii statement only where there is no overlap between the proposed carve-out label * * * and the [brand's] use code." Pet. 6a. Thus, accurate use codes are "essential to the [Act's] operation." Pet. 29a.

B. The Act's counterclaim provision and the *Mylan* decision

Aware of brands' efforts to "block generic competition by making unwarranted claims to patent coverage" (Pet. 25a), Congress enabled generics "in a Paragraph IV suit to assert a counterclaim challenging the accuracy of the 'patent information' submitted to the FDA" (Pet. 6a). As Congress provided:

> (I) In general.—If * * * the [NDA] holder * * * for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the [ANDA] applicant, the [ANDA] applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) of this section on the ground that the patent does not claim either—
>
> > (aa) the drug for which the application was approved; or
> >
> > (bb) an approved method of using the drug.

21 U.S.C. § 355(j)(5)(C)(ii)(I).

This provision was not always part of the Act; and in 2002 the Federal Circuit ruled in *Mylan Pharma-*

ceuticals, Inc. v. *Thompson*, 268 F.3d 1323 (Fed. Cir. 2001), that Hatch-Waxman did not authorize private actions to correct inaccurate patent listings. The generic there (Mylan) had filed a Section viii statement representing that a listed patent did not claim a use for which Mylan sought approval. When the FDA asked for clarification of the patent's scope, the brand responded that its patent *did* claim that use, prompting rejection of Mylan's Section viii statement. Mylan then sued, alleging that the brand's patent information was inaccurate. Describing Mylan's claim as "analogous to those barred in [a] long line of cases precluding private rights of action," the court rejected it. *Id.* at 1332. The decision, however, prompted both regulatory and legislative action.

C. The FDA's Regulations

The FDA acted first, amending its regulations in June 2003 to clarify the "need for accurate and detailed information related to the approved methods of use claimed in [listed] patent[s]." 68 Fed. Reg. at 36682. These "*Submission of Patent Information*" regulations contain special rules for method patents that claim one or more approved methods of using the listed drug. 21 C.F.R. § 314.53. Brands must submit a description of each approved method of using the drug (or, if appropriate, the labeled indication specifying the recommended use) claimed by its patent:

> (P) Information on each method-of-use patent including the following:
>
> > (1) Whether the patent claims one or more approved methods of using the approved drug product and a description of each approved method of use or indication and related patent claim of the patent being submitted;

> (2) Identification of the specific section of the approved labeling for the drug product that corresponds to the method of use claimed by the patent submitted; and
>
> (3) *The description of the patented method of use as required for publication.*

Id. § 314.53(c)(2)(ii)(P) (emphasis added).[5]

FDA "Form 3542," whereby NDA holders submit such patent descriptions, confirms that use codes must track the method patent's scope:

> The use code designates a method of use patent that claims the approved indication or use of a drug product. Each approved use claimed by the patent should be separately identified in this section and contain adequate information to assist * * * ANDA applicants in determining whether a listed method of use patent claims a use for which the * * * ANDA applicant is not seeking approval.

Pet. 211a-214a; 68 Fed. Reg. at 36682-36683.

Acting on comments from the Federal Trade Commission (FTC), the FDA also required brands to attest to the accuracy of patent information under penalty of perjury, cautioning them that knowingly filing false information violates 18 U.S.C. § 1001. 68 Fed. Reg. at 36686. But even criminal sanctions are insufficient to deter some companies. Accordingly, just months later, Congress undertook to "close loopholes in the law and end the abusive practices in the pharmaceutical industry * * * which have cost con-

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[5] Before 2003, the FDA merely requested a declaration that the NDA holder's patent covered a drug or approved use thereof. 59 Fed. Reg. 50338, 50363 (Oct. 3, 1994).

sumer billions," by allowing generics sued for infringement "to file a counterclaim to have the brand drug company * * * correct the patent information in FDA's Orange Book." 149 Cong. Rec. 31200 (Nov. 23, 2003) (Sen. Schumer).

Congress acted "with full awareness of the agency's interpretation of ['patent information']." Pet. 37a. The FDA's chief counsel twice testified concerning those regulations.[6] And as Senator Schumer, a leading sponsor, stated: "The bill provides a critical complement to the work the FDA has done in clarifying its regulations on patent listing, but it goes much further." *Legislative and Regulatory Responses to the FTC Study on Barriers to Entry in the Pharmaceutical Marketplace: Hrg. Before S. Comm. on Judiciary*, 108th Cong. 19 (2003); accord 149 Cong. Rec. S8690 (daily ed. June 26, 2003) (Sen. Hatch); *id.* at S8197 (daily ed. June 19, 2003) (Sen. Frist). Thus, in late 2003—six months after the FDA published its final rule—Congress enacted the counterclaim provision quoted above, employing the term "patent information" defined in the regulations.

D. Novo's New Drug Application and Caraco's Abbreviated New Drug Application

Novo holds an NDA for repaglinide, a diabetes drug sold as PRANDIN. Novo's patent on the repaglinide compound expired in 2009. Pet. 7a.

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[6] *FTC Study: Generic Drug Entry Prior to Patent Expiration: Hrg. Before S. Comm. on Judiciary*, 108th Cong. 5-20 (June 17, 2003) (statement of D. Troy, Chief Counsel for FDA); *Examining the Senate And House Versions of the "Great Access to Affordable Pharmaceuticals Act": Hrg. Before S. Comm. on Judiciary*, 108th Cong. 7-10 (Aug. 1, 2003) (statement of D. Troy, Chief Counsel for FDA).

The patent-in-suit (the '358 patent), which expires in 2018, claims the use of "repaglinide in combination with metformin," another diabetes drug, to treat patients with type 2 diabetes. *Ibid.* This is one of three FDA-approved uses of repaglinide; the others include repaglinide by itself (monotherapy); and repaglinide combined with thiazolidinediones (TZDs). *Ibid.* But "Novo does not own patents claiming the other two approved methods of using repaglinide." Pet. 8a. And until 2009, Novo's use code described its patent as covering *only* the "use of repaglinide in combination with metformin to lower blood glucose." Pet. 45a.

In February 2005, Caraco became the first ANDA applicant seeking to sell generic repaglinide. *Ibid.* Because Caraco initially filed a Paragraph IV certification, its proposed label had to list all FDA-approved uses of repaglinide. *Supra* n.4. In June 2005, Novo sued Caraco for patent infringement.

E. Novo's revised use code and the FDA's ruling on Caraco's Section viii application

Novo originally alleged that any generic label that referenced the repaglinide-metformin combination would induce infringement. At the FDA's urging, however, Caraco invoked Section viii, "declaring that Caraco was not seeking approval for the repaglinide-metformin combination therapy" and asking to carve out of the label any reference thereto. Pet. 8a.[7]

Based on Novo's first use code, the FDA ruled that Caraco's carve-out label would be proper. Pet. 8a. But in "'response to th[is] section viii ruling,'" Novo

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[7] Caraco filed a "split certification"—a Paragraph IV certification as to the non-method claims and a Section viii certification as to the method claims. Pet. 45a n.16.

amended its code to read: "a method for improving glycemic control in adults with type 2 diabetes mellitus." Pet. 49a, 45a. As "Novo admitted," "[t]he FDA did not direct or request that Novo change its use code"; "nor was [this] required under FDA regulations." Pet. 47a-48a (citing Novo's counsel).[8]

Based on Novo's new use code, the FDA "reversed itself and rejected Caraco's proposed labeling carveout"—requiring Caraco to include the patented repaglinide-metformin combination on its label. Thus, by misrepresenting the scope of its patent, Novo manufactured a claim that Caraco's label would induce infringement—effectively extending its patent on the repaglinide *compound*, which expired in 2009, to *unpatented uses* of that compound until 2018.

Caraco thus filed a counterclaim, seeking partial summary judgment and an injunction. Noting that its use code "seriously misrepresents the approved method of use covered by" the '358 patent, the district court enjoined Novo to restore its original use code. Pet. 70a. Novo's new use code is "so broad as to incorrectly suggest that the '358 patent generically covers three (3) different FDA-approved methods of use of repaglinide," the court explained, when "the first two (2) uses are not covered." Pet. 68a. The parties then agreed to postpone trial on issues of patent validity and enforceability, pending resolution of Novo's appeal.[9]

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[8] The FDA requested a new *label* for Novo's product; the use code describes the *patent*, not the label. *Ibid.*

[9] After the ruling below, the parties tried those issues before Judge Cohn. The district court has not yet ruled, but the outcome will not affect the suitability of this case for certiorari. See *infra* Part I.

F. The Federal Circuit's divided ruling

In a ruling that spawned three opinions, a divided Federal Circuit panel (Rader, Clevenger, Dyk, JJ.) reversed.

First, reading the phrase "*an* approved method of use" to mean "*any* approved method of use," the majority (per Rader, J.) held that a counterclaim is available "only if the listed patent does not claim *any* approved methods of using the listed drug." Pet. 12a (emphasis added). Although the word "any" appears elsewhere in the same provision (§ 355(j)(5)(C)(ii)(II)), the court never discussed this language, finding "no ambiguity in the statut[e]." Pet. 12a. Second, the majority held that the term "patent information" is limited to "an erroneous patent number or expiration date" and "does not extend to the use code narrative." Pet. 15a-16a.

In Judge Rader's view, a generic can use "a Paragraph IV lawsuit" to prove that its "use will not overlap with * * * the patented use." Pet. 14a. But Judge Clevenger, who concurred, was "not as certain" that "Paragraph IV litigation will cleanly resolve the dispute." Pet. 19a. As he recognized, "Caraco can no longer assert that its proposed labeling does not infringe." Pet. 20a. And although he blamed the FDA for purportedly creating the problem—on the mistaken understanding that "FDA's request that Novo change its labeling" required changing the *use code*—he acknowledged that the outcome "upset the careful balance of interests" embodied in the Act. *Ibid.*

Judge Dyk dissented, explaining that "the text is clear" in light of "the overall operation of the statutory scheme." Pet. 41a. "[I]nterpreting 'an approved method' * * * to mean 'any' approved method," he ob-

served, is "fundamentally inconsistent with the Supreme Court's admonition * * * that '[u]ltimately, context determines meaning.'" Pet. 39a.

On the "patent information" issue, Judge Dyk believed the majority's reading was contrary to the text, the FDA's interpretation, and *Chevron*—"even if the language of the statute is ambiguous, and not (as I urge) plainly contrary to the majority's interpretation." Pet. 30a, 33a. Further, because "Congress utilized the FDA's interpretation of 'patent information' * * * with full awareness," he believed that interpretation was "binding." Pet. 37a-38a.

Judge Dyk also clarified that the FDA did not cause "Caraco's predicament"—citing Novo's admission that "FDA did not require [a new use code]" and explaining that "absolutely nothing in the statute or regulations * * * required Novo to change the use code to track [its label]." Pet. 47a-48a. But he agreed with Judge Clevenger that generics are "left without any remedy to correct an erroneous Orange Book listing" for "a method of use patent." Pet. 51a. Moreover, he found the majority's approach to be "notably inconsistent with the approach adopted by our sister circuit in another recent Hatch-Waxman Act case, *Teva Pharms. USA, Inc.* v. *Sebelius*, 595 F.3d 1303 (D.C. Cir. 2010)." Pet. 51a.

G. The dissent from the denial of rehearing

Over Judges Gajarsa's and Dyk's dissent, en banc review was denied. As Judge Gajarsa explained, "[b]oth constructions" adopted by the majority—its "overly narrow construction of 'patent information' and [its] overly broad construction of 'an approved method of using the drug'"—"are irreconcilable with

pre-existing FDA regulations, the text of the [Act], and Congressional intent." Pet. 59a.

Furthermore, brands now have "every incentive to follow Novo's lead and draft exceedingly broad use codes"—thus "subverting Section viii carve-out statements." Pet. 62a, 60a. By "leav[ing] generic drug manufacturers without a remedy to challenge inaccurate listings with respect to method of use patents," Judge Gajarsa explained, the majority's ruling "render[s] section viii a dead letter." Pet. 59a, 62a.

Judge Gajarsa also objected that, "[w]ithout even requesting the views of the FDA, the majority opinion refuses to give effect to [its] interpretation of an important statutory term." Pet. 63a. This was "especially troubling given Congress's explicit approval of those regulations." *Ibid.*

In sum, holding "that counterclaim relief is not available because the [patent in suit] covered at least one approved use * * * effectively allows a patent holder to extend its monopoly to unpatented uses." Pet. 62a. This "absurd result * * * contravenes the intent of Congress in adopting the counterclaim"—"a critical provision of the [Act]." Pet. 63a, 59a.

REASONS FOR GRANTING THE PETITION

The Federal Circuit's fractured 2-1 ruling compels immediate review. The question presented is not only recurring, but critically important to the $300 billion pharmaceutical industry, to consumers needing low-cost drugs, and to the FDA—whose longstanding interpretation of "patent information" was ratified by Congress in 2003, but invalidated below without the agency's input. In one fell swoop, the Federal Circuit: read Section viii out of existence (Part I); overruled the FDA's definition of "patent information," ignoring *Chevron* and placing the FDA in an intractable administrative bind (Part II); created a critical inconsistency with the D.C. Circuit on how to read the counterclaim provision (Part III); and violated numerous precedents of this Court, including precedent interpreting Hatch-Waxman itself (Part IV). This Court's review is urgently needed.

I. The decision below threatens FDA approval for myriad generics that seek to market their products solely for non-patented uses under Section viii.

When Congress passed the Hatch-Waxman Act, it established two principal means of obtaining FDA approval to market generic drugs: Paragraph IV certifications, which assert that any Orange Book-listed patents are invalid or not infringed by the generic's product, prompting full-blown litigation; and Section viii statements, which seek to *avoid* such litigation where the generic asks to market its product solely for uses *not* covered by any patent. As Judges Dyk and Gajarsa understood, the decision below leaves generics "without any remedy to correct an erroneous Orange Book listing with respect to a method of use

patent"—"rendering Section viii a dead letter." Pet. 51a, 62a.

1. When a generic files a Paragraph IV certification, that filing constitutes an artificial act of patent infringement that obligates the brand either to sue or risk FDA approval of generic marketing. 35 U.S.C. § 271(e)(2). If the brand sues, FDA approval is stayed for 30 months or until the generic prevails—in which case the agency may approve the ANDA. 21 U.S.C. § 355(j)(5)(B)(iii). Further, if the generic was the first filer, it receives 180 days of market exclusivity before other generics can go to market. *Id.* § 355(j)(5)(B)(iv). But generics must generally prevail in court to obtain FDA approval under Paragraph IV.

Section viii, by contrast, is designed to avoid litigation. It "facilitates the approval and marketing of lower-cost generic drugs for uses no longer protected by a patent." Pet. 59a. "[W]here a patent claims at least one, but not all, approved methods of using a drug" (Pet. 13a-14a), Section viii allows the generic to certify that the patent "does not claim a use for which the applicant is seeking approval." 21 U.S.C. § 355(j)(2)(A)(viii). The generic submits a carve-out label that does not refer to the patented uses (Pet. 6a); and if the FDA approves it, litigation is unnecessary. But even if it is the first Section viii filer, a generic cannot obtain 180 days of marketing exclusivity under Section viii.

Paragraph IV and Section viii thus offer tradeoffs. Prevailing in Paragraph IV suits holds the promise of a non-infringement or invalidity ruling—enabling the generic to sell its drug for *all* approved uses—and for first filers 180 days of marketing exclusivity. Section viii offers only the ability to market drugs for *some*

approved uses, with no prospect of marketing exclusivity. Yet section viii avoids the delays and "hazard[s] of sparking costly litigation." *Teva*, 595 F.3d at 1305. It is therefore "essential to the [Act's] operation." Pet. 29a.

2. "The majority opinion * * * eviscerates Section viii." Pet. 62a (Gajarsa, J., dissenting). It creates "every incentive" for brands "to follow Novo's lead and draft exceedingly broad use codes," "thereby insulating themselves from generic competition." *Ibid.*

First, the ruling forces generics to defend costly and protracted patent litigation, when they should be free to sell their drugs for non-infringing uses without setting foot in court. Still worse, generics must fight with one hand tied behind their backs. That is because the unavailability of Section viii requires generics to use the same label as the brand—which includes the patented use, and is by definition infringing.[10] Thus, to prevail in Paragraph IV litigation, generics that seek approval only for non-infringing uses must prove *invalidity*—a much higher burden—when they should not even have to litigate.

The ruling below therefore gives brands "the advantage of [stalling generic approval under Paragraph IV]" without "the disadvantage of [Section viii's carve-out label]"—which would preclude any showing of infringement. See *Eli Lilly*, 496 U.S. at 671-672. It is "most implausible that Congress" would intend this, and there is no evidence—let alone "strong evidence"—that it did. *Id.* at 672-673. Indeed, the majority's interpretation is "at odds with one of the most basic interpretive canons, that '[a] statute should be

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[10] Caraco therefore stipulated to infringement.

construed so that effect is given to all its provisions, so that no part will be inoperative or superfluous, void or insignificant.'" *Corley* v. *United States*, 129 S. Ct. 1558, 1566 (2009).

It is no answer to say that some generics might overcome these hurdles, reaching the market by winning a Paragraph IV suit. Some may win, some may lose, but the point of Section viii is that *no* generic should have to litigate whether an unexpired method patent is valid whenever there are other approved and unpatented uses of the drug. Being forced to litigate is a direct affront to Congress's aim of speeding the introduction of generic drugs where, if a carve-out label *were* available, there could be no infringement. Yet the ruling below, and Novo's actions, force Caraco to litigate validity, greatly delaying Caraco's ability to sell *concededly* non-infringing drugs.[11]

Nor does a generic wrongly denied a carve-out label possess an adequate remedy in suing the FDA. Such a suit would likely fail, since the FDA lacks any "statutory basis for a substantive review of patents," and courts have repeatedly "upheld [the agency's] determination that [its] role with respect to patent listings is ministerial." 68 Fed. Reg. at 36683 (collecting decisions); accord Pet. 50a-51a. But again, subjecting generics to the delay and expense involved in bringing such suits undermines Section viii's purpose—*avoiding* litigation where non-infringement is indisputable. It also undermines the Act's ultimate goal:

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[11] That being forced to defend Paragraph IV litigation itself eviscerates Section viii is one of many reasons why review of this case is needed now, and why the interlocutory nature of the decision below should not stand in the way of certiorari.

"get[ting] generic drugs into the hands of patients at reasonable prices—fast." *Barr Labs.*, 930 F.2d at 76.

Second, by eliminating the Act's check on allowing brands to overstate their patents, the decision below "effectively allows a patent holder to extend its monopoly to unpatented uses." Pet. 62a. This would be problematical in any context, but it is especially troubling under Hatch-Waxman. In other markets, competitors that wish to sell allegedly infringing products can launch at risk and litigate later. But selling drugs requires FDA approval. *Eli Lilly*, 496 U.S. at 670-671. Thus, if brands can bottle up the approval process, generics are excluded from the market even absent risk of infringement (due to a carve-out label). The counterclaim serves as a critical check on such (well-documented) "gam[ing] of the system," but the ruling below renders that provision "a virtual nullity." Pet. 59a; see Federal Trade Commission, *Generic Drug Entry Prior to Patent Expiration* 46, 52 (July 2002) (identifying multiple "categories of patents listed in the Orange Book rais[ing] significant listability issues").

3. This problem is not isolated. It arises every time generics file Section viii ANDAs for drugs with more than one FDA-approved use.

This is increasingly common, as patents on blockbuster drug compounds expire and brands seek to extend their monopolies via method patents—a process known as "evergreening." Bouchard, et al., *Empirical Analysis of Drug Approval-Drug Patenting Linkage for High-Value Pharmaceuticals*, 8 Nw. J. Tech. & Intel. Prop. 174, 182 (2010) ("that pharmaceutical companies are focusing more on evergreening older products and on incremental drug development rather

than breakthrough drug development suggests that firms may be leveraging legal loopholes favouring enhanced patent protection for drugs with low innovative value"). And consumers are directly affected. As the Department of Health and Human Services notes: "In 2010 to 2014, a number of blockbusters are projected to go off patent," and "[t]he greatest and most certain potential for increased savings [to consumers] * * * lies in the increased availability of generic drugs through patent expirations." *ASPE Issue Brief: Expanding the Use of Generic Drugs* 2, 13 (Dec. 1, 2010).[12]

The importance of the question presented is confirmed by recent statistical analysis. For example, in the wake of "the hubbub over Patent Use Codes ('PUCs') since the [decision below]," one study "analyze[d] the growth of [use codes]." Karst, *Analysis Shows Patent Use Codes Have Doubled Since August 2003* (July 8, 2010).[13] As this study found, only "25 [use codes] were listed" in the Orange Book in 1988, when use codes were initiated. *Ibid.* But today, "a grand total of 1062 [use codes]" have been listed; and "532 new [use codes] have been designed by NDA holders" since 2003. *Ibid.* "[A]lthough free to use 'old' [use codes]," brands "appear to be favoring the creation of new [ones]," which lets them "tailor" the code to their liking. *Ibid.*

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[12] Available at: http://aspe.hhs.gov/sp/reports/2010/GenericDrugs/ib.pdf.

[13] Available at: http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2010/07/analysis-shows-patent-use-codes-have-doubled-since-august-2003--by-kurt-r-karst-httpwwwhpmcomvattorneycfmrid22.html.

The number of new use codes created by brands has doubled since 2003. *Ibid.* And there is every reason to expect use codes to grow exponentially if the decision below is left undisturbed. As Judge Gajarsa observed, brands "have found another way to game the system"—"by submitting overbroad and inaccurate use codes." Pet. 60a. "With the majority's blessing [brands] now have every incentive to follow Novo's lead"—"subverting Section viii carve-out statements" and "rendering Section viii a dead letter." Pet. 60a, 62a.

Not surprisingly, the Federal Circuit's ruling "has grabbed the attention of the drug industry"—a $300 billion industry. Sandburg, *Patent Use Codes May Still Block Generics as FDA Looks for Alternatives*, The Pink Sheet 18 (Oct. 18, 2010); Clinton & Mozeson, *The Pharm Exec 50* 71, Pharmaceutical Executive (May 2010). As one leading practitioner, who "emphasized the significance of the Novo case," noted: ""This is an issue that is reverberating through the industry and through all our practices."" Sandburg, *supra*, at 18; see also Sandburg, *"The Next Best Way to Block Generics" May Be Novo's Patent Use Code Switch*, The Pink Sheet 28-29 (June 7, 2010).

Review is therefore needed *now*.

II. By invalidating the FDA's "patent information" regulations, the ruling below undercut the FDA's ability to administer the Act.

Review is likewise warranted because the Federal Circuit's ruling threatens the FDA's administration of the Act. Without soliciting the agency's views, the court invalidated pre-existing regulations governing the submission of "patent information"—regulations Congress ratified in 2003. That throws a wrench in

the FDA's ability to enforce provisions "essential to the [Act's] operation." Pet. 29a. And the FDA's counsel has publicly cited these enforcement problems, confirming the urgency of review.

1. In 2003, when considering how to implement the Act's "patent information" requirement, the FDA took extensive public comments and considered three main responses to the use code problem. *First*, it considered substantively reviewing use codes, by means "rang[ing] from hiring patent lawyers" to "development of a full administrative hearing process." 68 Fed. Reg. at 36683. *Second*, it considered "permit[ting] each ANDA * * * applicant to make its own independent decision on whether a listed method-of-use patent claims the use for which the ANDA applicant seeks approval." *Id.* at 36682. *Third*, it considered "requir[ing] the NDA applicant * * * to identify specifically the approved uses claimed by the method of use patent"—the approach ultimately adopted. *Ibid.*

The FDA favored the third approach for several reasons. For instance, it lacked any "statutory basis" for conducting substantive patent analysis. *Id.* at 36683. The Act imposes "short time frames" for publishing Orange Book listings, and these mandates "do not contemplate a substantive agency review of the scope of the patent." *Ibid.* Further, the FDA "lack[s] both the resources and the expertise to resolve [patent] matters." *Ibid.* Indeed, "[a] fundamental assumption of the Hatch-Waxman Amendments is that the courts are the appropriate mechanism for the resolution of disputes about the scope and validity of patents"—since they "have the experience, expertise, and authority." *Ibid.*

Deferring to *generics'* Section viii submissions, by contrast, could create inappropriate incentives in the opposite direction. If generics "could always avoid the possibility of a 30-month stay [of FDA approval] by asserting in a section viii statement that certain labeling for which the applicant is seeking approval is not protected by a listed method-of-use patent," "there would be little reason for any [ANDA] applicant to submit a paragraph IV certification for a method-of-use patent." *Id.* at 36682. Furthermore, requiring brands to submit use code information is "more efficient and accurate," since brands have better access to relevant information. *Id.* at 36683.

Whatever approach it took, however, the FDA was clear that "accurate and detailed information related to the approved methods of use" was "essential" to fulfilling its statutory duty to "expedite [its] review of ANDA * * * applications that do not seek approval for all the approved uses." 68 Fed. Reg. at 36682, 36685. Citing the "case law" and prior "questions about what aspects of the approved drug was claimed by a listed use patent," the FDA recognized that "submission of inappropriate patent information" had "led to confusion and then to litigation over an ANDA applicant's obligation to submit either a paragraph IV certification * * * or a 'section viii' statement." *Id.* at 36682. "To effectively implement the [Paragraph IV] certification and section viii statement provisions," the FDA concluded, "it is necessary that an NDA holder submit more specific information on the approved methods of use protected by a submitted patent. *Only with this information* can we determine what submission is required of [generics]." *Id.* at 36682, 36683 (emphasis added). The final rule therefore required

brands to submit use code information. 21 C.F.R. § 314.53(c)(2)(ii)(P)(1).

Congress not only ratified the FDA's approach; it went "much further," "provid[ing] a critical complement to the work the FDA has done in clarifying its regulations on patent listing" by empowering courts to resolve disputes concerning overbroad use codes. *Barriers to Entry Hearing, supra* , at 19.

2. The ruling below ignores all of this, sending the FDA back to square one. "Patent information" is now limited to the "patent number or expiration date," and the counterclaim is limited to "suits to correct or delete" such numbers and dates. Pet. 15a-16a. This reading, however, deprives the agency of information it "must have" to "expedite [its] review of ANDA * * * applications that do not seek approval for all the approved uses." 68 Fed. Reg. at 36682. Whereas the FDA's 2003 changes sought to "reduce confusion and help curb [brands'] attempts to take advantage of this [approval] process" (*ibid.*), invalidating those changes will have the opposite effect.

Since the decision below, while "the FDA is assessing ways to alter how it handles patent use codes following charges they are being used to derail the approval of generics," "a straightforward solution so far has eluded the agency." Sandburg, *supra*, at 18. Indeed, the FDA's own counsel has publicly cited "the significance of the case" and expressed concern about the enforcement problems it creates. *Ibid.* As Elizabeth Dickinson, senior counsel in the FDA's Office of Chief Counsel, recently explained, the difficulty created by the Federal Circuit "is going to be complicated to resolve." *Ibid.* As she recounted, the FDA is considering "the best way forward," but the alterna-

tive approaches have drawbacks and implementing them is "a recipe for marketplace confusion, in addition to complications in terms of intellectual property rights." *Ibid.*

FTC Commissioner Thomas Rosch has likewise cited the decision, stating that Judge Dyk's dissent "took a view that was more consistent with promoting competition."[14] As these statements of public officials confirm, review is needed now.

III. The decision below is inconsistent with recent D.C. Circuit precedent.

Review is also warranted because, as Judge Dyk noted, the ruling below is "notably inconsistent with the approach adopted by [the D.C. Circuit] in another recent Hatch-Waxman case, *Teva Pharmaceuticals USA, Inc.* v. *Sebelius*, 595 F.3d 1303 (D.C. Cir. 2010)." Pet. 51a.

Teva analyzed a Hatch-Waxman provision allowing generics to *forfeit* their 180-day exclusivity rights. The FDA argued that Hatch-Waxman allows *brands* to trigger forfeiture when generics do not market their products within a certain time after "patent information * * * is withdrawn by the [brand]." 21 U.S.C. § 355(j)(5)(D)(i)(I). Under this view, "after a generic has filed a paragraph IV certification," the brand may "announce that in fact the challenged patent is not one that protects the drug," and "ask the FDA to 'delist' the patent, thus purporting to pull the

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[14] *The Antitrust/Intellectual Property Interface: Thoughts on How To Best Wade Through the Thicket in the Pharmaceutical Context Before the World Generic Medicine Congress* 13 (Nov. 17, 2010), available at: http://www.ftc.gov/speeches/rosch/101117roschworldspeech.pdf.

rug from under the paragraph IV certification." 595 F.3d at 1305.

The FDA approved this maneuver, but the D.C. Circuit rejected it, holding that a brand cannot "unilaterally deprive the generic of its exclusivity." *Id.* at 1317. In support, the court cited both the counterclaim provision and the overall "statutory structure." *Id.* at 1315, 1316.

"*The FDA may not * * * change the incentive structure adopted by the Congress*," the court explained, "for the agency is bound not only by the ultimate purposes Congress has selected but by the means it has deemed appropriate." *Id.* at 1316 (quotation omitted). Finding "*not a single cogent reason* why Congress might have permitted brand manufacturers to trigger [forfeiture] by withdrawing a challenged patent, outside the counterclaim scenario," the court held that "[n]o forfeiture can take place unless the brand manufacturer brings an infringement suit against the generic and either loses on the merits or enters an unfavorable settlement." *Id.* at 1317. This result promoted Hatch-Waxman's purpose of providing generics "'the certainty of receiving a period of marketing exclusivity.'" *Id.* at 1316 (citation omitted).

The decision below is in serious tension with *Teva*, which turns on the counterclaim's role in providing "certainty" for generics. Like the brand in *Teva*, Novo seeks "to pull the rug from under" Caraco's Section viii statement. The difference is that here the brand maneuver was not *de-listing* the patent, but *changing its description*. And it worked. The FDA reversed itself and rejected Caraco's carve-out label.

In holding that no counterclaim is available, the majority below not only flouts the counterclaim's text, which allows generics both to "correct" *and* "delete" patent information (21 U.S.C. § 355(j)(5)(C)(ii)(I)); it also "*change[s] the incentive structure adopted by the Congress.*" 595 F.3d at 1316. Courts are "bound not only by the ultimate purposes Congress has selected" (providing certainty), but "by the means it has deemed appropriate" (providing a counterclaim to "correct" patent information). *Ibid.* And this is especially clear absent any "cogent reason why Congress might have" precluded brands from improperly listing patents, but not from describing them too broadly—either way, extending them beyond their scope.

The inconsistency between *Teva* and the ruling below—on a matter of great importance to the FDA, industry, and consumers—confirms the need for review.

IV. Certiorari is warranted because the panel's splintered decision rewrites a key provision of the Hatch-Waxman Act.

In addition to nullifying Section viii and the FDA's "patent information" regulations—inviting manipulation of FDA drug approval and delaying competition—the statutory construction employed below violates myriad precedents of this Court. *First*, it substitutes the word "any" for "an"—rewriting the text, which authorizes counterclaims whenever there is "an approved method of using the drug" that the listed patent "does not claim." *Second*, it ignores the FDA's definition of "patent information," which Congress ratified and in all events warrants *Chevron* deference. These errors—on a recurring issue "essential to the [Act's] operation" (Pet. 29a)—underscore the importance of review.

A. The majority misconstrued the Act's plain text and ignored the cardinal rule that statutory language must be read in context.

1. As countless decisions hold, "'[t]here is a basic difference between filling a gap left by Congress' silence and rewriting rules that Congress has * * * specifically enacted.'" *Lamie* v. *United States Trustee*, 540 U.S. 526, 538 (2004) (citation omitted). Yet the majority below rewrote the statute by "read[ing] 'an approved method' as 'any approved method.'" Pet. 12a. That was flatly incorrect, particularly in light of "the structure of the * * * Act taken as a whole." *Eli Lilly*, 496 U.S. at 669.

Novo admits that there is "an approved method of using the drug" that its patent "does not claim." Yet the majority ignored this sensible reading of the plain text. Instead, it "detect[ed] no ambiguity" because, "[w]hen an indefinite article is preceded and qualified by a negative, standard grammar generally provides that 'a' means 'any.'" Pet. 12a.

The majority believed that substituting "any" for "an" left the Act unchanged. But the fact that "an," when qualified by a negative, *can* mean "any" does not mean it *generally* means "any." As Judge Dyk noted, the majority invoked *secondary* definitions of "an." Pet. 41a. And as one leading commentator on English usage has observed, use of "any" in "negative assertions * * * creates an *emphatic* negative, meaning 'not at all' or 'not even one.'" Garner, *A Dictionary of Modern American Usage* 45 (1998) (emphasis added). Indeed, "any" is "an expansive word" demanding an "expansive reading." *New York* v. *EPA*, 443 F.3d 880, 887 (D.C. Cir. 2006). Inserting "any"

into the text, therefore, was not a neutral interpretive decision; it changed the statute's meaning. Moreover, as discussed below, Congress used "any" elsewhere in the same provision, confirming that it did *not* intend "an" to mean "any" here.

2. This reveals the deeper problem with the ruling below: It ignores the cardinal rule that "[u]ltimately, context determines meaning." *Johnson* v. *United States*, 130 S. Ct. 1265, 1270 (2010). It is a "fundamental principle of statutory construction (and, indeed, of language itself) that the meaning of a word cannot be determined in isolation, but must be drawn from the context in which it is used." *Deal* v. *United States*, 508 U.S. 129, 132 (1993). By ignoring this principle, the majority ran through no fewer than five contextual "stop signs."

First, the phrase "an approved method" appears in a provision entitled "[c]ounterclaim to infringement action," which affords relief to a generic able to show that "the patent does not claim" a certain method of use. By design, this provision asks not whether the *brand* can show that its patent *claims* "an approved method," but whether the *generic* can point to "an approved method" that the patent "*does not* claim." This error led the majority to read the statute backwards—as if the brand raised the counterclaim. That violated this Court's teaching that, "'[i]n ascertaining the plain meaning of the statute, the court must look to the particular statutory language at issue, as well as the language and design of the statute as a whole.'" *Household Credit Servs.* v. *Pfennig*, 541 U.S. 232, 239 (2004).

An illustration confirms this. Suppose A writes to B with news that she had another child. In relating

the challenges of having more children, A adds that "my taxes are higher than they should be because I did not claim an exemption." Read in context, this statement does not suggest that A did not claim *any* exemption—only that she did not claim an exemption *for the latest child*. If B ignored the context and concluded that A did not claim *any* exemptions, we would not say A's use of the phrase "did not claim an exemption" was ambiguous. We would say B read it in isolation. The same is true of the majority's reading of "an approved method."

Second, to read "an" as "any" is particularly inappropriate given that "any" appears elsewhere in the same provision. 21 U.S.C. § 355(j)(5)(C)(ii)(II) ("any civil proceeding"). So "Congress knew how" to express other meanings. *Central Bank* v. *First Interstate Bank*, 511 U.S. 164, 176-177 (1994). And as the bill's lead sponsor explained: "[T]o close the loopholes * * * the devil is in the details. * * * Change an 'and' to an 'a,' to a 'the' and you go from huge savings to huge costs." *Hrg. Before Cmte. on Judiciary*, *supra*, 108 Cong. 15 (Sen. Schumer).

Third, the Act authorizes counterclaims "to *correct or* delete patent information," but the majority "render[ed] superfluous" the term "correct." See *Astoria Fed. Sav. & Loan Ass'n* v. *Solimino*, 501 U.S. 104, 112 (1991). That is, brands may list only patents that claim the drug or an approved method of using it; and under the majority's view, a counterclaim is available only where the patent claims *neither*—the problem in *Mylan*. But in cases like *Mylan*, the patent should not have been listed *at all*, and the proper remedy is "deleting" it. Pet. 32a (Dyk, J., dissenting).

Thus, "[v]iewing [Congress's] overruling of *Mylan* as limited to complete delisting would be inconsistent with the explicit statutory language, which provides for correction of Orange Book information" as well. *Ibid.* And even if "[*Mylan*] prompted the *proposal* of [the counterclaim provision]," "whether that alone accounted for its *enactment* is quite a different question." *Eli Lilly*, 496 U.S. at 670. The counterclaim provision's broad text confirms that Congress meant to close other "loopholes in the law and end abusive practices * * * by allowing a generic applicant * * * to file a counterclaim to * * * correct the patent information." 149 Cong. Rec. 31200 (2003) (Sen. Schumer).

Fourth, Section viii and the counterclaim provision work together and use similar language—one refers to a patent that "does not claim *a* use" approved for the branded drug, the other to a patent that "does not claim *an* approved method of us[e]." There is no reason to read these provisions inconsistently, such that the counterclaim means "*any*" use and Section viii means "*a*" use.

Finally, even if the Act were viewed as reflecting "legislative imprecision" (*Eli Lilly*, 496 U.S. at 679), there is no reason why Congress would want courts to "delete" misleading patent information when brands' patents claim *no* approved use, but not to "correct" misleading patent descriptions used to block marketing for *some subset of* non-infringing uses. Under this Court's Hatch-Waxman precedent, it takes "strong evidence to persuade [the Court] that" Congress "should enact provisions" that "create an effective extension of the patent term." *Id.* at 670, 672, 673. Such evidence of "implausible substantive intent" is lacking here. *Id.* at 679. And that is especially clear when the counterclaim is read in light of Section viii

and "the structure of the 1984 Act taken as a whole." *Id.* at 669.

B. In contravention of *Chevron*, the majority erroneously invalidated the FDA's settled interpretation of "patent information."

The majority's ruling that the Act's undefined use of "patent information" is limited to "the patent number and expiration date," not "use codes" (Pet. 15a-16a) is also contrary to the FDA's considered interpretation—and violates *Chevron* v. *NRDC, Inc.*, 468 U.S. 867 (1984).

In 2003, the "FDA promulgated a regulation [entitled '*Submission of Patent Information*'] * * * requir[ing] a [brand] to submit not only the patent number and the expiration date, but also the use code narratives." Pet. 16a. Congress then acted "with full awareness of the agency's interpretation," yet the majority ignored this "compelling evidence of legislative adoption." Pet. 37a & n.11.

The majority dismissed the fact that the FDA defined "patent information" before the counterclaim was enacted as an "'opaque timing observation[].'" Pet. 16a. But there was nothing opaque about it. If Congress meant to overrule the published definition of "patent information," it would have said so. "Congress * * * does not alter the fundamental details of a regulatory scheme in vague terms or ancillary provisions—it does not * * * hide elephants in mouseholes." *Whitman* v. *Am. Trucking Ass'ns, Inc.*, 531 U.S. 457, 468 (2001). The counterclaim thus *implements* the FDA's definition.

Even apart from *Chevron*, the FDA's interpretation is correct. By filing a counterclaim, what a generic can "correct or delete" is "patent information

submitted by the holder under [§ 505](b) or (c)." 21 U.S.C. § 355(j)(5)(C)(ii)(I). Because § 505(b) and (c) mention only the patent number and expiry, the majority read "patent information" as limited to those items. But this rewrites the text, which speaks of "patent information *submitted* * * * *under* subsection (b) or (c)," not "patent information *referenced in*" those subsections.

By using the term "under," Congress anticipated that the agency would require additional patent information to administer the statute. And as the FDA stated shortly before Congress acted, "accurate and detailed information related to the approved methods of use" is "essential" to its ability to "expedite [its] review of ANDA * * * applications that do not seek approval for all the approved uses"—a statutory mandate. 68 Fed. Reg. at 36682, 36685. Far from being "at odds with the [statute's] plain language" (Pet. 16a), the FDA's interpretation tracks it. But at a minimum, its interpretation is reasonable, warranting *Chevron* deference. Pet. 33a-36a.

In sum, the majority failed to see that "[s]licing a statute into phrases while ignoring their contexts—the surrounding words, the setting of the enactment, the function a phrase serves in the statutory structure—is a formula for disaster." *Herrmann* v. *Cencom Cable Assocs.*, 978 F.2d 978, 982 (7th Cir. 1992). This Court's review is needed to avert that disaster.

CONCLUSION

For the foregoing reasons, the petition for a writ of certiorari should be granted.

Respectfully submitted.

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DECEMBER 2010

APPENDIX

APPENDIX A

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

2010-1001

NOVO NORDISK A/S and NOVO NORDISK, INC.,

Plaintiffs-Appellants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD., and SUN PHARMACEUTICAL INDUSTRIES, LTD.,

Defendants-Appellees.

Mark A. Perry, Gibson, Dunn & Crutcher LLP, of Washington, DC, argued for plaintiffs-appellants. With him on the brief were Josh A. Krevitt, of New York, New York; Wayne Barsky, of Los Angeles, California; and Michael A. Sitzman, of San Francisco, California.

James F. Hurst, Winston & Strawn LLP, of Chicago, Illinois, argued for defendants-appellees. With him on the brief were Charles B. Klein and Scott H. Blackman, of Washington, DC; David S. Bloch, of San Francisco, California. Of counsel was Andrew Nichols, of Washington, DC.

Appealed from: United States No. 2010-1001 District Court for the Eastern District Michigan

Senior Judge Avern Cohn

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2010-1001

NOVO NORDISK A/S and NOVO NORDISK, INC.,

Plaintiffs-Appellants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD.,
and SUN PHARMACEUTICAL INDUSTRIES, LTD.,

Defendants-Appellees.

Appeal from the United States District Court for the Eastern District of Michigan in case no. 2:05-CV-40188, Senior Judge Avern Cohn.

DECIDED: April 14, 2010

Before RADER, CLEVENGER, and DYK, Circuit Judges.

Opinion for the court filed by Circuit Judge RADER. Concurring opinion filed by Circuit Judge CLEVENGER. Dissenting opinion filed by Circuit Judge DYK.

The United States District Court for the Eastern District of Michigan entered an injunction directing Novo Nordisk A/S and Novo Nordisk, Inc. (collectively, "Novo") to request the U.S. Food and Drug Administration ("FDA") to replace Novo's patent use code U-968 listing for Prandin® in the Orange Book with the former U-546 listing. Because Caraco Pharmaceutical Laboratories, Ltd. ("Caraco") does not have a statutory basis to assert a counterclaim re-

questing such injunctive relief, this court reverses and vacates the injunction.

I.

This case arises under the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified at 21 U.S.C. §§ 355, 360cc; 35 U.S.C. §§ 156, 271), as amended by the Medicare Prescription Drug Improvement and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003) (collectively, the "Hatch-Waxman Act"). The Hatch-Waxman Act strikes a balance between two potentially competing policy interests—inducing pioneering development of pharmaceutical formulations and methods and facilitating efficient transition to a market with low-cost, generic copies of those pioneering inventions at the close of a patent term. See *Andrx Pharms., Inc.* v. *Biovail Corp.*, 276 F.3d 1368, 1371 (Fed. Cir. 2002).

Title 21 prohibits sale of a new drug without FDA approval. 21 U.S.C. § 355(a). To obtain that approval, a pioneering manufacturer must file a new drug application ("NDA"), containing clinical studies of the drug's safety and efficacy. 21 U.S.C. § 355(b)(1). As part of the NDA process, the manufacturer must also identify all patents that claim the drug or a method of use:

> The applicant shall file with the application *the patent number* and *the expiration date* of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a

> person not licensed by the owner engaged in the manufacture, use, or sale of the drug.

21 U.S.C. § 355(b)(1)(G) (emphases added).

> If *the patent information described in subsection (b)* of this section could not be filed with the submission of an application under subsection (b) of this section . . . , the holder of an approved application shall file with the Secretary *the patent number* and *the expiration date* of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.

21 U.S.C. § 355(c)(2) (emphases added).

The FDA has authority to promulgate regulations for the efficient enforcement of these provisions. 21 U.S.C. § 371. Under those regulations, a pioneering manufacturer files with the FDA the patent number and the expiration date of any applicable patents by submitting Form 3542a ("Patent Information Submitted with the Filing of an NDA, Amendment, or Supplement") or Form 3542 ("Patent Information Submitted Upon and After Approval of an NDA or Supplement"). 21 C.F.R. § 314.53 (2009). If the patent claims one or more methods of using the NDA drug, Forms 3542a and 3542 require a description of each of those processes. *Id.* This description is commonly known as the "use code narrative." The FDA assigns a unique number, known as a "use code," to each description. The FDA publishes a list of drugs, along with the applicable patents and their associated use

codes, in its Approved Drug Products With Therapeutic Equivalence Evaluations, commonly known as the "Orange Book."

A manufacturer that seeks to market a generic copy of these listed drugs may submit an abbreviated new drug application ("ANDA"). 21 U.S.C. § 355(j). The ANDA process streamlines FDA approval by allowing the generic manufacturer to rely on the safety and efficacy studies of a drug already listed in the Orange Book upon a showing of bioequivalence. 21 U.S.C. § 355(j)(2)(A)(iv).

As part of the ANDA process, a generic manufacturer must make a certification addressing each patent identified in the Orange Book pertaining to its drug. 21 U.S.C. § 355(j)(2)(A)(vii). Specifically, the generic manufacturer must select one of four alternatives permitting use of the patented product or process: (I) no such patent information has been submitted to the FDA; (II) the patent has expired; (III) the patent is set to expire on a certain date; or (IV) the patent is invalid or will not be infringed by the manufacture, use, or sale of the generic drug. 21 U.S.C. § 355(j)(2)(A)(vii).

Often pharmaceutical formulations have multiple uses and applications. After expiration of the patent on the composition itself, only some of those uses may enjoy continued protection as patented methods. If a generic manufacturer wishes to seek FDA approval for a use not covered by a method-of-use patent for a listed drug, it must make a "section viii statement." 21 U.S.C. § 355(j)(2)(A)(viii). Along with the section viii statement, the generic manufacturer must submit a proposed label to the FDA that does not contain the patented method of using the listed drug. When con-

sidering approval of these requests for a use not covered by a patent, the FDA relies on the applicable patent's use code narrative to determine the scope of the patented method. *Applications for FDA Approval to Market a New Drug*, 68 Fed. Reg. 36676, 36682 (June 18, 2003). The FDA approves the section viii statement only where there is no overlap between the proposed carve-out label submitted by the generic manufacturer and the use code narrative submitted by the pioneering manufacturer. *Id.*

The Hatch-Waxman Act facilitates early resolution of disputes between pioneering and generic manufacturers. To achieve this objective, the Act makes a Paragraph IV certification into an act of patent infringement. 35 U.S.C § 271(e)(2). A generic manufacturer that files a Paragraph IV certification must give notice to the patentee and the NDA holder and provide a detailed basis for its belief that the patent is invalid or not infringed. 21 U.S.C. § 355(j)(2)(B)(i). The patentee then has forty-five days to sue the generic manufacturer for infringement. 21 U.S.C. § 355(j)(5)(B)(iii). If the patentee does not sue, the FDA may approve the ANDA. If the patentee sues, the FDA may not approve the ANDA until expiration of the patent, resolution of the suit, or thirty months after the patentee's receipt of notice, whichever is earlier. 21 U.S.C. § 355(j)(5)(B)(iii). The court entertaining this suit has discretion to order a shorter or longer stay if "either party to the action fail[s] to reasonably cooperate in expediting the action." *Id.*

The Hatch-Waxman Act enables a generic manufacturer in a Paragraph IV suit to assert a counterclaim challenging the accuracy of the "patent information" submitted to the FDA:

> [The ANDA] applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) of this section on the ground that the patent does not claim either–
>
> > (aa) the drug for which the application was approved; or
> >
> > (bb) an approved method of using the drug.

21 U.S.C. § 355(j)(5)(C)(ii)(I). This counterclaim provision was not part of the original Hatch-Waxman Act. Rather the Medicare Prescription Drug Improvement and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003) added this counterclaim provision to permit challenges to patent information at the FDA. The interpretation of this counterclaim provision is the central issue in this case.

II.

Novo markets and distributes the drug repaglinide under the brand name PRANDIN. PRANDIN is an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (non-insulin dependent diabetes mellitus). The FDA has approved PRANDIN for three uses: (1) repaglinide by itself (i.e., monotherapy); (2) repaglinide in combination with metformin; and (3) repaglinide in combination with thiazolidinediones ("TZDs"). Novo Nordisk, Inc. holds the approved NDA for PRANDIN.

The Orange Book lists two patents for PRANDIN. U.S. Patent No. RE 37,035 (the "'035 patent") claims, *inter alia*, the chemical composition of repaglinide. The '035 patent expired on March 14, 2009. U.S. Pat-

ent No. 6,677,358 (the "'358 patent") claims, *inter alia*, repaglinide in combination with metformin:

> A method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin.

'358 patent, claim 4. The '358 patent expires on June 12, 2018. Novo Nordisk A/S owns the '358 patent. Novo does not own patents claiming the other two approved methods of using repaglinide to treat type 2 diabetes. The FDA initially assigned the '358 patent the use code "U-546–Use of repaglinide in combination with metformin to lower blood glucose."

On February 9, 2005, Caraco filed an ANDA for the drug repaglinide. The ANDA initially contained a Paragraph III certification for the '035 patent and a Paragraph IV certification for the '358 patent. On June 9, 2005, Novo initiated an infringement action against Caraco. In April 2008, Caraco stipulated that its ANDA would infringe the '358 patent if it included a label that discussed the combination of repaglinide and metformin. At around the same time, Caraco submitted an amended ANDA with a Paragraph IV certification for the '358 patent and a section viii statement declaring that Caraco was not seeking approval for the repaglinide-metformin combination therapy. The FDA indicated that it would approve Caraco's proposed carve-out label. Novo moved for reconsideration on the ground that allowing the carve-out would render the drug less safe and effective.

On May 6, 2009, Novo submitted an amended Form 3542 for PRANDIN in which Novo updated its use code narrative for the '358 patent. The FDA removed the use code U-546 from the Orange Book for

PRANDIN and substituted the new use code "U-968–A method for improving glycemic control in adults with type 2 diabetes mellitus." The FDA then denied Novo's request for reconsideration as moot in light of the new use code. According to the FDA, the factual predicate on which the FDA's permissive carve-out determination had rested no longer applied. The FDA then disallowed Caraco's section viii statement, because its proposed carve-out label overlapped with the use code U-968 for the '358 patent. As a result, Caraco's current label now includes the repaglinide-metformin combination therapy, which is stipulated to infringe claim 4 of the '358 patent.

On June 11, 2009, Caraco amended its answer and counterclaim. Caraco added a counterclaim under 21 U.S.C. § 355(j)(5)(C)(ii), requesting an order requiring Novo to change the use code for the '358 patent in reference to PRANDIN from U-968 to U-546. Caraco claimed that the use code U-968 was overbroad because it incorrectly suggested that the '358 patent covered all three approved methods of using repaglinide even though it claimed only one approved method. Caraco also added a patent misuse defense, asserting that Novo misrepresented the scope of the '358 patent in its use code narrative.

On June 29, 2009, Novo moved to dismiss Caraco's new counterclaim and to strike the patent misuse defense. The district court denied Novo's motions. Caraco then moved for summary judgment on both the new counterclaim and the patent misuse defense. On summary judgment, the district court granted Caraco's motion on the counterclaim and declined to address the patent misuse defense. The district court found that Novo had improperly filed an overbroad use code narrative for the '358 patent. On September

25, 2009, the district court entered the following injunction:

> Novo Nordisk is hereby directed by mandatory injunction under 21 U.S.C. § 355(j)(5)(C)(ii)(1)(bb) to correct within twenty (20) days from the date of this Order and Injunction its inaccurate description of the '358 patent by submitting to FDA an amended Form FDA 3542 that reinstates its former U-546 listing for Prandin and describes claim 4 of the '358 patent in section 4.2b as covering the "use of repaglinide in combination with metformin to lower blood glucose."

Novo Nordisk A/S v. *Caraco Pharm. Labs., Ltd.*, Case 2:05-cv-40188, slip. op. 1-2 (E.D. Mich. Sept. 25, 2009).

Given the urgency of Novo's situation, Novo filed a motion in this court for an expedited appeal from the district court's order. This court granted Novo's motion to expedite briefing. Novo also filed a motion for a stay of the injunction pending appeal and a stay of trial court proceedings. This court ordered a stay of the injunction pending disposition of this appeal but declined to stay trial court proceedings. Because the district court had jurisdiction under 28 U.S.C. §§ 1331 and 1338(e), this court has jurisdiction under 28 U.S.C. § 1292(c)(1).

III.

This court reviews the grant of an injunction for an abuse of discretion. *Cross Med. Prods., Inc.* v. *Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1301-02 (Fed. Cir. 2005). To the extent that an injunction is premised upon an issue of law, such as statutory interpretation, this court reviews that issue without

deference. See *Sanofi-Synthelabo* v. *Apotex, Inc.*, 470 F.3d 1368, 1374 (Fed. Cir. 2006).

Statutory construction "begins with 'the language of the statute." *Hughes Aircraft Co.* v. *Jacobson*, 525 U.S. 432, 438 (1999) (quoting *Estate of Cowart* v. *Nicklos Drilling Co.*, 505 U.S. 469, 475 (1992)). This court derives the plain meaning of the statute from its text and structure. *Electrolux Holdings, Inc.* v. *United States*, 491 F.3d 1327, 1330 (Fed. Cir. 2007) (citation omitted). If the statutory language is unambiguous, the inquiry ends. *Id.* Nevertheless, this court may "look at the legislative history 'only to determine whether a clear intent contrary to the plain meaning exists." *Sharp* v. *United States*, 580 F.3d 1234, 1238 (Fed. Cir. 2009) (quoting *Glaxo Operations UK Ltd.* v. *Quigg*, 894 F.2d 392, 396 (Fed. Cir. 1990)). To overcome the plain meaning of the statute, the party challenging it must establish that the legislative history provides "an 'extraordinary showing of contrary intentions." *Id.* (quoting *Garcia* v. *United States*, 469 U.S. 70, 75 (1984)).

IV.

The Hatch-Waxman Act provides a limited counterclaim to a generic manufacturer in a Paragraph IV infringement action. The Act authorizes the generic manufacturer to assert a counterclaim "on the ground that *the patent does not claim* either (aa) the drug for which the application was approved; or (bb) *an approved method of using the drug*.' 21 U.S.C. § 355(j)(5)(C)(ii)(I) (emphases added).

Novo and Caraco agree that the '358 patent claims only one of the three approved methods of using PRANDIN (i.e., repaglinide in combination with metformin). Novo asserts that the counterclaim is avail-

able only if the '358 patent does not claim any approved methods. Caraco argues that it is entitled to the counterclaim because the '358 patent does not claim two of the approved methods of PRANDIN use. In other words, Novo reads "an approved method" in the counterclaim statute as "any approved method" while Caraco reads it as "all approved methods."

This court detects no ambiguity in the statutory language. When an indefinite article is preceded and qualified by a negative, standard grammar generally provides that "a" means "any." See, *e.g.*, American Heritage Dictionary of the English Language 1 (4th Ed. 2006) (defining "a" as "[a]ny" in the example "not a drop to drink"); Random House Webster's Unabridged Dictionary 1 (2d ed. 2001) (defining the indefinite article "a" as "any" or "a single" in the example "not a one"); see also *Barnhart* v. *Thomas*, 540 U.S. 20, 26 (2003) (adopting a construction that is "quite sensible as a matter of grammar") (citation omitted).

The rest of the counterclaim provision also does not support Caraco's interpretation. In the context of this case, the statutory language "an approved method of using the drug" refers to the approved methods of using the listed drug, PRANDIN. This language cannot refer to the methods of using Caraco's generic drug, because the FDA has not yet approved Caraco's ANDA. Therefore, the Hatch-Waxman Act authorizes a counterclaim only if the listed patent does not claim any approved methods of using the listed drug.

Although the statutory language on its face presents no ambiguities, this court nonetheless examines the legislative history to make sure that it does not

contain any clear intent to the contrary. Before the amendment to the Hatch-Waxman Act in 2003, private litigants could not challenge FDA submissions at all. *Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 349 (2000). Novo and Caraco agree that the counterclaim provision responded to this court's decision in *Mylan Pharms., Inc.* v. *Thompson*, 268 F.3d 1323 (Fed. Cir. 2002). In *Mylan*, the Orange Book listed a patent as covering the FDA-approved drug BuSpar. *Id.* at 1330-31. Mylan, a generic manufacturer, asserted that the patent "did not claim BuSpar or an approved method of using BuSpar." *Id.* at 1331. This court held that Mylan did not have a private cause of action to delist the allegedly irrelevant patent from the Orange Book. *Id.* The 2003 amendment used exact language from *Mylan* in the new counterclaim provision. This choice of legislative language suggests that the 2003 Amendment sought to correct the specific issue raised in *Mylan*, i.e., to deter pioneering manufacturers from listing patents that were not related at all to the patented product or method. Thus, the language selected for this Amendment supports this court's interpretation that "an approved method" means "any approved method." A patent listing that covers one amongst several approved methods of using a formulation protects that patented method and thus bears a direct relation to the purpose of Orange Book listings. This court does not detect a situation such as the one occurred in *Mylan*.

This case also suggests that this court should address the relationship between section viii and the counterclaim provision. Section viii addresses scenarios where a patent claims at least one, but not all, approved methods of using a drug. See 21 U.S.C. § 355(j)(2)(A)(viii). This court recognizes that a broad

use code covering all uses of a pharmaceutical could require generic manufacturers to prove specifically that their use will not overlap with and infringe the patented use. This proof, under Hatch-Waxman procedures, will take the form of a Paragraph IV lawsuit. In that context, the generic may provide proof that their use will not cause infringement of the patented use. This court perceives that the Hatch-Waxman Act will thus ensure that a generic drug for non-patented purposes will not be used for patented purposes via a simple section viii certification. Instead, the generic manufacturer will need to alleviate the risk of infringement or induced infringement in a proceeding that fully tests for infringement and its implications, including potential health and safety risks. Thus, the Act again facilitates efficient resolution of disputes concerning potential overlapping of protected and unprotected uses. The Act seeks to strike a balance of the pioneering and generic manufacturers' interests.

As Judge Clevenger points out, Caraco's real complaint should lie with the FDA, not with Novo. Had it not been for the FDA's regulatory action, Caraco could have asserted in a Paragraph IV lawsuit that its proposed labeling did not infringe the '358 patent. It was the FDA, not Novo, that tipped the careful balance in the favor of pioneering manufacturers.

V.

As further indication of balancing interests and creation of an efficient dispute resolution mechanism, this court notes that the Act, by its terms, does not allow generic manufacturers to counterclaim unless the listed patent bears no relation to the listed drug. To be more specific, the terms of the counterclaim provision do not authorize an order compelling the

patent holder to change its use code narrative. The counterclaim provision states that a generic manufacturer can request an order compelling "the holder to correct or delete *the patent information* submitted by the holder under subsection (b) or (c)." 21 U.S.C. § 355(j)(5)(C)(ii)(I) (emphasis added). Subsection (b) requires a pioneering manufacturer to submit "*the patent number* and the expiration date of any patent . . . which claims a method of using such drug." 21 U.S.C. § 355(b)(1) (emphases added). Subsection (c) states that "[i]f *the patent information* described in subsection (b) of this section could not be filed with the submission of an application," the holder "shall file with the Secretary *the patent number* and *the expiration date* of any patent . . . which claims a method of using such drug." 21 U.S.C. § 355(c)(2) (emphases added).

Thus, the Act defined the term "patent information" as "the patent number and the expiration date." See *Valley Drug Co.* v. *Geneva Pharms. Inc.*, 344 F.3d 1294, 1296-97 (11th Cir. 2003) (referring to the patent number and the expiration date as "this patent information"). The reference in subsection (c) to "the patent information described in subsection (b)" could only mean the patent number and the expiration date, because no other "patent information" appears in the statute. Therefore, to maintain consistency in the statutory terms, "the patent information" in the counterclaim provision must also mean the patent number and the expiration date. *Envtl. Def.* v. *Duke Energy Corp.*, 549 U.S. 561, 574 (2007) (noting that the identical words used in the same act are presumed to have the same meaning). Thus, the counterclaim provision only authorizes suits to correct or delete an erroneous patent number or expiration

date. The authorization does not extend to the use code narrative. Once again, this careful use of language suggests that the Act facilitates efficient resolution of disputes over the potential overlap of patented and unpatented uses in the form of a Paragraph IV suit.

Approximately six months before the 2003 Amendment, the FDA promulgated a regulation concerning the "Submission of Patent Information" in which it requires a pioneering manufacturer to submit not only the patent number and the expiration date, but also the use code narratives and other patent-related information on Forms 3542a and 3542. See 21 C.F.R. § 314.53. This regulation appeared to include the use code narrative under the broader heading of "patent information." Although this regulation preceded the 2003 Amendment, it did not change the meaning of the statutory use of the term "patent information." As this court has clarified, "[s]uch opaque timing observations hardly amount to a 'most extraordinary showing of contrary intentions,' especially when the language of the statute trumpets its meaning by itself." *Wyeth* v. *Kappos*, 591 F.3d 1364, 1372 (Fed. Cir. 2010). The counterclaim provision does not mention the FDA regulations or in any way suggest adoption of a meaning for "patent information" broader than the express statutory definition. Moreover, this court owes "no deference is due to agency interpretations at odds with the plain language of the statute itself." *Pub. Employees Ret. Sys.* v. *Betts*, 492 U.S. 158, 171 (1989). As discussed above, this broader definition would upset the careful balance that requires a full resolution of the potential infringement issues involved in overlapping patented and unpatented uses.

The legislative history does not add any clarity to the meaning of "patent information." During the floor debate, Senators occasionally referred to the need to correct "patent information." See, *e.g.*, 149 Cong. Rec. S15746 (daily ed. Nov. 24, 2003) (statement of Sen. Schumer) (The counterclaim provision may "delist the patent or correct the patent information in FDA's Orange Book."). This court must read these statements to use the term "patent information" consistent with the express statutory definition. Accordingly, to preserve the Act's careful balance and to enforce the language of the statute, the explicit definition of "the patent information" as "the patent number and the expiration date" controls.

VI.

Caraco argues that in case this court does not find that Caraco is entitled to a counterclaim, this court should affirm the district court's injunction under the doctrine of patent misuse. Because the judicial doctrine of patent misuse creates an unusual circumstance where an infringer can escape the consequences of its infringing conduct because the victim of that tort may have used its patent rights to gain an unfair competitive advantage against an unrelated third party, this court examines such allegations with particularity. See, *e.g.*, *C.R. Bard* v. *M3 Sys.*, 157 F.3d 1340, 1372-73 (Fed. Cir. 1998) ("Although the law should not condone wrongful commercial activity, the body of misuse law and precedent need not be enlarged into an open-ended pitfall for patent-supported commerce."). For instance, the doctrine may apply where the patentee's misconduct toward unrelated parties amounted to unfair market benefits beyond the scope of the patent. See *Mallinckrodt, Inc.* v. *Medipart, Inc.*, 976 F.2d 700, 704 (Fed. Cir. 1992). In

any event, in this case, the district court, apparently recognizing the rarity of this situation, expressly declined to address the doctrine of patent misuse. Without any finding to review, this court declines to adjudicate this issue in the first instance. See *Ecolab, Inc.* v. *FMC Corp.*, 569 F.3d 1335, 1352 (Fed. Cir. 2009).

VII.

This court therefore reverses the district court's grant of summary judgment on Caraco's attempted, but unsuccessful, counterclaim and vacates the injunction ordering Novo to correct its use code for the '358 patent listed in the Orange Book for PRANDIN.

REVERSED and VACATED.

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2010-1001

NOVO NORDISK A/S and NOVO NORDISK, INC.,

Plaintiffs-Appellants,

v.

CARACO PHARMACEUTICAL
LABORATORIES, LTD.,
and SUN PHARMACEUTICAL INDUSTRIES, LTD.,

Defendants-Appellees.

Appeal from the United States District Court
for the Eastern District of Michigan
in case no 2:05-CV-40188, Senior Judge Avern Cohn.

CLEVENGER, Circuit Judge, concurring.

I agree with Judge Rader's analysis of the relevant statutory provisions in this case and therefore join the opinion he writes for the court. I am not as certain as Judge Rader that the ongoing Paragraph IV litigation will cleanly resolve the dispute between the parties.

The dissent masks the cause for the dispute between the parties. Novo did nothing that was illegal or forbidden. FDA voluntarily requested a change to the approved indications for PRANDIN® which required Novo to use FDA's new approved labeling. The change also permitted Novo to revise its use code as the relevant FDA form, "Patent Information Submitted Upon and After Approval of an NDA or Supplement," expressly instructed Novo to "[s]ubmit the description of the approved indication or method of use that you propose FDA include as the 'Use Code' in the Orange Book." Novo changed its use code to match

the new PRANDIN® indication. Nothing in the record suggests that Novo is responsible for the labeling change, which, given the statutory and regulatory framework, happens to benefit Novo at Caraco's expense.

If not for FDA's request that Novo change its labeling to the present broad indication, everything would have worked properly under the relevant statutes. As Judge Rader notes, the "efficient dispute resolution mechanism" was in play. Caraco filed its ANDA for repaglinide, and by making its Paragraph IV certification had committed the statutory act of infringement. Novo followed with its infringement suit. Caraco was prepared to defend on the grounds that its proposed use of repaglinide would not induce infringement of the '358 patent. Caraco also filed a section viii statement in light of the then-approved labeling and use code for PRANDIN®, and proposed carve-out language in its labeling to signify its proposed noninfringing use of repaglinide. Caraco was thus set to get FDA approval to bring its generic drug to market and to defend itself in Novo's Paragraph IV suit.

But FDA, acting independently, gummed up the works. By requiring a single broad indication for repaglinide as part of the approved labeling, FDA created a situation where Caraco can no longer assert that its proposed labeling does not infringe the '358 patent. It remains to be seen what impact FDA's action will have on Caraco's ability to defend itself in the ongoing Paragraph IV litigation, but FDA's regulatory action threatens to impair Caraco's ability to disprove infringement. FDA thus may have inadvertently upset the careful balance of interests repre-

sented by the efficient dispute resolution mechanism Congress created in the Hatch-Waxman Act.

The dissent's fix would be to have United States District Courts dictate to FDA what indications should be used on the prescribed labeling for approved drugs, even though there is nothing illegal, or even incorrect, about Novo's current use code. There is no basis for a counterclaim to correct or delete the patent information submitted by Novo. If a fix is in order under the circumstances of this case, it lies with the FDA and Congress to understand the consequences of changing the approved repaglinide labeling to a single broad indication, and corresponding use code, and to remedy the situation. Laying blame on Novo is wrong.

The counterclaim statute, which the dissent would expand beyond its literal reach, was designed to cure the situation presented in *Mylan*. Congress has not addressed the fact situation presented in this case. Congress is the appropriate entity to readjust, if necessary, the delicate balance it has struck between original drug manufacturers and their generic counterparts.

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DYK, Circuit Judge, dissenting.

In 2003, Congress enacted the counterclaim provision of the Hatch-Waxman Act in order to prevent manipulative practices by patent holders with respect to the Orange Book listings. These practices were designed to delay the onset of competition from generic drug manufacturers. See Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, § 1101(a)(2)(C), 117 Stat. 2066, 2452 (codified at 21 U.S.C. § 355(j)(5)(C)(ii)) ("the counterclaim amendment"). In my view, the majority, in reversing the district court, now construes the statute contrary to its manifest purpose and allows the same manipulative practices to continue in the context of method patents. The amendment was designed to permit the courts to order correction of information published in the Orange Book, yet under the majority's opinion, erroneous Orange Book method of use

information cannot be corrected. I respectfully dissent.

I.

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act, commonly known as the "Hatch-Waxman Act." Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified at 21 U.S.C. § 355 and scattered sections of 35 U.S.C.). Under the Hatch-Waxman Act, Congress required the Food and Drug Administration ("FDA") to maintain and publish a list of patents associated with approved drugs and methods of use. See *id.* § 102(a)(1). The FDA has implemented this provision by publishing this list in its publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"). See 21 C.F.R. § 314.53(c)(2)(i)(O).[1] The statute is complicated, but its operation in the present context is not.

A

Under the Food, Drug, and Cosmetic Act ("FDCA"), a drug manufacturer must secure approval from the FDA for the sale of any drug in interstate commerce. 21 U.S.C. § 355(a). To do so, the manufacturer files a New Drug Application ("NDA") with the FDA to secure approval for a "new drug," 21 U.S.C. § 355(b)(1), a term which encompasses a new use for an existing drug, see 21 C.F.R. § 310.3(h)(4). The ap-

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[1] See also Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying that a Patent Claiming a Drug Is Invalid or Will Not Be Infringed, 68 Fed. Reg. 36,676, 36,686 (June 18, 2003) (codified at 21 C.F.R. pt. 314) ("Report and Order Accompanying the Patent Listing Rule").

plication requires that the manufacturer specify the drug (or drugs) in question and the proposed method (or methods) of use. See 21 C.F.R. § 314.53(b)-(c). The drug cannot be sold until the FDA has approved the drug for the particular method of use, 21 U.S.C. § 355(a), (b)(1), and the method of use is required to appear on the label, 21 U.S.C. § 352(f); 21 C.F.R. pt. 201, *id.* § 314.125(b)(8). Section 355(b) also requires the NDA filer to list all patents "with respect to which a claim of patent infringement could reasonably be asserted" by patent number and expiration date with its NDA application, 21 U.S.C. § 355(b)(1), while section 355(c)(2) requires NDA applicants to provide the same information with respect to patents issuing after the NDA application was approved, *id.* § 355(c)(2). This information, referred to as "information submitted . . . under subsection (b) or (c)" or "patent information," is published in the Orange Book. *Id.* § 355(b)(1), (c)(2).

A generic manufacturer may piggyback on the safety and efficacy data the original drug manufacturer submitted in its NDA, and may seek approval for an identical method of use for its identical generic product by submitting an "Abbreviated New Drug Application," or "ANDA." See *id.* § 355(j). If a patent is listed in the Orange Book for a drug or method of use covered by the NDA, the generic is generally required to certify that the patent has expired or is invalid or will not be infringed by the sale or use of the drug for which the ANDA is submitted. *Id.* § 355(j)(2)(A)(vii). In what is called a "paragraph IV" certification regarding noninfringement and invalidity, approval is stayed pending the outcome of court

litigation to determine infringement and validity[2] Recognizing that some NDAs would cover both uses covered by a patent and uses not covered by a patent, Congress enacted "section viii," which allows the ANDA applicant to limit its application to unpatented uses, and to secure approval for those unpatented uses. *Id.* § 355(j)(2)(A)(viii); H.R. Rep. No. 98-857 pt. 1, at 22 (1984), *as reprinted in* 1984 U.S.C.C.A.N. 2647, 2655.

Some NDA filers realized that they could block generic competition by making unwarranted claims to patent coverage, for example, by listing in the Orange Book a patent for a drug or method of use when in fact the patent was clearly inapplicable. The FDA repeatedly declined to police the Orange Book listings,[3] and before the enactment of the counterclaim provision in 2003, we held that the courts could not do so through declaratory judgments. See *Mylan*

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[2] Where the applicant makes this paragraph IV certification, the patentee has forty-five days to bring suit for infringement of the patent that is the subject of the generic manufacturer's certification, and the approval of the ANDA is stayed for a period of thirty-months (or until the resolution of the infringement suit, whichever is shorter). See 21 U.S.C. § 355(j)(5)(B)(iii). The first ANDA applicant to make a paragraph IV certification benefits from a 180-day period of marketing exclusivity, *id.* § 355(j)(5)(B)(iii)(IV)(iv), a provision intended encourage generic manufacturers to undertake challenges to patents claimed to cover brand drugs. See *Teva Pharms. USA, Inc.* v. *Sebelius*, 595 F.3d 1303, 1318 (D.C. Cir. 2010).

[3] The FDA has consistently held the position that its role in listing patents in the Orange Book is "ministerial," and that establishing an administrative process for reviewing patents, assessing patent challenges, and de-listing patents would involve patent law issues that are beyond its expertise and authority. See, *e.g.*, Report and Order Accompanying the Patent Listing Rule, 68 Fed. Reg. at 36,683.

Pharms., Inc. v. *Thompson*, 268 F.3d 1323, 1332- 33 (Fed. Cir. 2001).

Congress responded by enacting the counterclaim amendment as part of the "Greater Access to Affordable Pharmaceuticals Act" ("Gregg-Schumer Bill"), enacted in 2003. S. 1225, 108th Cong. (2003). The counterclaim amendment provides:

> (ii) Counterclaim to infringement action.—
>
> > (I) In general.—If an owner of the patent or the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent *or a use of which is claimed by the patent* brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to *correct or delete the patent information submitted by the holder under subsection (b) or (c) of this section* on the ground that the patent does not claim either—
> >
> > > (aa) the drug for which the application was approved; or
> > >
> > > (bb) *an approved method of using the drug*.

21 U.S.C. § 355(j)(5)(C)(ii) (emphases added). Thus, the amendment allows an ANDA applicant, who is defending against a patent infringement suit brought by the holder of the NDA, to assert a counterclaim to correct or delete the Orange Book "patent information submitted . . . under subsection (b) or (c)" on the ground that the patent does not claim "the drug for which the application was approved" or "an approved method of using the drug." We have not previously

construed this provision. The majority now holds that the counterclaim provision is unavailable to correct erroneous method of use information in the Orange Book—on two separate grounds.

II.

A

In my view, the majority has misconstrued the term "patent information submitted . . . under subsection (b) or (c)." *Id.* § 355(j)(5)(C)(ii)(I). In the majority's view, method of use information is not "patent information." The majority construes the term as limited to the patent number and expiration date: "[T]he Act defined the term 'patent information' as 'the patent number and the expiration date.'" Majority Op. at 13. There is, in fact, no definition of "patent information" in the statute, and in reaching this construction, the majority ignores critical statutory language. The statute requires the NDA applicant to

> file with the application the patent number and the expiration date of any patent *which claims the drug for which the applicant submitted the application* or *which claims a method of using such drug* and *with respect to which a claim of patent infringement could reasonably be asserted* if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.

21 U.S.C. § 355(b)(1) (emphases added). Thus, the statute requires the NDA applicant to list patents claiming a drug or method of use "with respect to which a claim of patent infringement could reasonably be asserted." In other words, the statute on its face contemplates that the scope of the patent must be accurately described and that the patent must be

related to the drug or method of use for which the NDA application is submitted.[4] The statute does not require the listing of patent numbers and expiration dates in the abstract. It contemplates the description of the scope of the patent and of the relationship between the patent and the drug or the method of use; the description of that scope and relationship is itself "patent information." The statute requires that this information be published, stating that the Secretary "shall publish information submitted under the two preceding sentences." *Id.*

Other provisions of the statute also contemplate that the ANDA filer will be able to understand the scope of the patent and to *relate* the patent information to the drug or drugs being claimed and the method or methods of use being claimed. See *id.*

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[4] Subsection (b) refers to patent information submitted with an NDA application; subsection (c) describes the requirements for the submission of patent information after an NDA has already been filed. The patent listing and publication requirements of 21 U.S.C. § 355(c)(2) parallel those in § 355(b)(1):

> If the patent information described in subsection (b) of this section could not be filed with the submission of an application under subsection (b) of this section because the application was filed before the patent information was required under subsection (b) of this section or a patent was issued after the application was approved under such subsection, the holder of an approved application shall file with the Secretary the patent number and the expiration date of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. . . . Upon the submission of patent information under this subsection, the Secretary shall publish it.

§ 355(b)(1). Describing the scope of the patent and relating the listed patents to the drug or method of use is essential to the operation of the statute, as the basic idea of the patent listings in the Orange Book is to put ANDA applicants on notice regarding which listed drugs and methods of use may be copied and which drugs or method of use are patent protected, and to enable the ANDA filer to submit an appropriate certification as required by law. The statute requires an ANDA applicant to provide, as part of the application,

> (vii) a certification, in the opinion of the applicant and to the best of his knowledge, *with respect to each patent which claims the listed drug* referred to in clause (i) or *which claims a use for such listed drug for which the applicant is seeking approval* under this subsection and *for which information is required to be filed under subsection (b) or (c) of this section*—
>
> (I) that such patent information has not been filed,
>
> (II) that such patent has expired,
>
> (III) of the date on which such patent will expire, or
>
> (IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted . . . .

Id. § 355(j)(2)(A)(vii) (emphases added). Similarly, the section viii certification provision also appears to contemplate that information submitted under subsection (b) or (c) will encompass information regarding

the patented method of use. The statute directs the ANDA applicant to submit,

> if with respect to the listed drug referred to in clause (i) *information was filed under subsection (b) or (c) of this section for a method of use patent* which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

Id. § 355(j)(2)(A)(viii). The statute plainly contemplates that "patent information" will include information that describes the scope of the patent and that relates the patent to the drug or method of use.

B

Quite apart from the fact that the majority's limiting interpretation is inconsistent with the statutory language and structure, the majority's interpretation is in my view untenable for other reasons.

First, the majority agrees that the counterclaim amendment was designed to overrule our decision in *Mylan*. Majority Op. at 11. In overruling *Mylan*, Congress viewed erroneous information as to the scope of the patent and its relationship to an approved drug or method of use as "patent information" that could be ordered corrected. The majority appears to suggest that the overruling of *Mylan* is limited to the precise facts of *Mylan*, namely, the situation in which correction of the error would require that the patent number be deleted entirely from the Orange Book. See *id.* The overruling would not apply to a situation in which other erroneous Orange Book information is involved, for example, where the patent is erroneously listed with respect to a particular drug or method of use, but is properly listed elsewhere in the

Orange Book. This ignores the context of the *Mylan* decision.

The first thing to understand is that the majority's description of the Orange Book likely bears no relationship to the actual document. The Orange Book is not a list of patents from which a particular patent could be excised. The Orange Book is a list of NDAs that associates particular patents with approved drugs or methods of use. Correction of an Orange Book listing does not strike a patent from a list, it strikes (or corrects) the listing that associates the patent with a particular NDA, approved drug, or method of use.

The problem in *Mylan* was that the Orange Book improperly described the scope of the patent and improperly related the patent to a drug and method of use not covered by the patent. In *Mylan*, Bristol-Myers Squibb ("Bristol") owned U.S. Patent No. 4,182,763 ("the '763 patent") directed to the treatment of anxiety through the administration of buspirone hydrochloride. 268 F.3d at 1327. The '763 patent was listed in the Orange Book in connection with that use but was about to expire. *Id.* Eleven hours before the patent's expiration, Bristol delivered to the FDA copies of U.S. Patent No. 6,150,365 (the "'365 patent"), which included a single method claim directed to the treatment of anxiety using a "metabolite" of buspirone.[5] *Id.* at 1327-28. Bristol sought to have the '365 patent listed in the Orange Book as covering

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[5] A metabolite is "[a] product of intermediary metabolism." *McGraw-Hill Dictionary of Scientific and Technical Terms* 1319 (6th ed. 2003). We held in *Hoechst-Roussel Pharms., Inc.* v. *Lehman*, 109 F.3d 756, 759 (1997), that a patent claiming either the active ingredient of a drug or a method of using that ingredient does not also cover metabolites of that ingredient.

buspirone and a method of using buspirone. *Id.* at 1328. *Mylan* and other ANDA applicants challenged the listing of the '365 patent on the ground that it only covered a metabolite of buspirone, and a method of using a metabolite of buspirone to treat anxiety. *Id.* After the FDA refused to correct the listing, Mylan filed suit for a declaratory judgment that Bristol improperly listed the '365 patent in the Orange Book as covering buspirone and the use of buspirone, and a preliminary injunction requiring Bristol to delist the '365 patent. *Id.* Reversing the district court, we held that there was no declaratory relief available to correct an erroneous Orange Book listing. *Id.* at 1332-33.

Thus, in *Mylan*, the accused infringer challenged the accuracy of the listing associating the patent with the approved method of use. Congress acted to provide a counterclaim action to correct such errors. Congress' concern with the proper listing of the patent in the Orange Book does not remotely suggest a myopic congressional focus on situations where the patent belonged nowhere in the Orange Book, as the majority suggests. Most significantly, viewing the overruling of *Mylan* as limited to complete delisting would be inconsistent with the explicit statutory language, which provides for correction of Orange Book information "on the ground that the patent does not claim . . . the drug for which the application was approved." 21 U.S.C. § 355(j)(5)(C)(ii)(I). The statute thus must allow correction of a misdescription of patent scope that includes a drug not covered by the patent and erroneous information about the relationship between the patent and the drug, even if the patent is properly listed elsewhere in the Orange Book. In other words the scope of the patent and its relationship to the drug must be "patent information."

Moreover, if "patent information" includes information as to the scope of the patent with respect to the drug and the relationship between the patent number and the drug, it must also include Orange Book information describing the scope of a method of use patent and linking the method of use to the patent. There is no basis in the statutory language or statutory purpose for distinguishing between drug information and method of use information. Either both must be "patent information," or neither must be patent information. In my view, all Orange Book information is "patent information."

Second, at the time the counterclaim provision was enacted in 2003, the FDA had adopted the Patent Listing Rule,[6] making clear that the agency had adopted a broad interpretation of "patent information submitted . . . under subsection (b) or (c)." That interpretation is entitled to *Chevron* deference even if the language of the statute is ambiguous, and not (as I urge) plainly contrary to the majority's interpretation. See *Chevron U.S.A. Inc.* v. *Natural Res. Def. Council*, 467 U.S. 837, 843-44 (1984). By the time of the counterclaim amendment in 2003, the FDA had adopted detailed requirements for the submission of "patent information" for both drugs and methods. The 2003 rule, published as a proposed rule in the *Federal Register* in late 2002[7] and finalized six months before

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[6] The full title of the final rule was: "Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying that a Patent Claiming a Drug Is Invalid or Will Not Be Infringed," 68 Fed. Reg. 36,676.

[7] See Applications for FDA Approval to Market a New Drug: Patent Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying

the counterclaim amendment, includes a section entitled "Submission of patent information" on the requirements for the listing of a patent in the Orange Book. See 21 C.F.R. § 314.53. The report accompanying the regulatory revision makes clear that the FDA is defining what constitutes "patent information" for purposes of subsections (b) and (c).[8] Additionally, the

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that a Patent Claiming a Drug Is Invalid or Will Not Be Infringed, 67 Fed. Reg. 65,448 (Oct. 24, 2002) ("Proposed Rule").

[8] The Report explains why it is promulgating the regulation, and in fact this is because of the existence of subsections (b) and (c):

> To explain why we (FDA) issued the proposal, we first describe how Federal law requires NDA applicants to file patent information and how that patent information can affect the approval of ANDA and 505(b)(2) applications. . . .
>
> Section 505(b)(1) of the act (21 U.S.C. 355(b)(1)) requires all NDA applicants to file, as part of the NDA, "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." Section 505(c)(2) of the act (21 U.S.C. 355(c)(2)) imposes a similar patent submission obligation on holders of approved NDAs when the NDA holder could not have submitted the patent information with its application.
>
> Under section 505(b)(1) of the act, we publish patent information after approval of an NDA application in our approved drug products list entitled "Approved Drug Products With Therapeutic Equivalence Evaluations." This list is known popularly as the "Orange Book" because of its orange-colored cover. If patent information is submitted after NDA approval, section 505(c)(2) of the act directs us to publish the information upon its submission.

report accompanying the Proposed Rule in 2002 confirms that the FDA's authority for the 2003 rule arises from not only the FDA's general authority to enforce the FDCA under 21 U.S.C. § 371, but also its authority to implement section 505 of the Hatch-Waxman Act, "including the patent listing and patent certification requirements" in section 505(b). See Proposed Rule, 67 Fed. Reg. at 65,457. The regulation itself provides that "patent information" includes 1) "[i]nformation on the drug substance (active ingredient) patent including . . . [w]hether the patent claims the drug substance that is the active ingredient in the drug product described in the new drug application or supplement," 2) "[i]nformation on the drug product (composition/formulation) patent including . . .

[w]hether the patent claims the drug product for which approval is being sought,"[9] and 3) "[i]nformation on each method-of-use patent including . . . [w]hether the patent claims one or more methods of using the drug product for which approval is being sought and a description of each pending method of use or related indication and related patent claim of the patent being submitted."[10]

Report and Order Accompanying the Patent Listing Rule, 68 Fed. Reg. at 36676.

[9] A "drug product" is a "finished dosage form . . . that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients." See 21 C.F.R. § 314.3. A "drug substance" is "an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body." *Id.*

[10] These listing requirements are described in 21 C.F.R. § 314.53(c)(2), while § 314.53(c)(1) provides: "An [NDA] applicant . . . shall submit the required patent information described

The NDA applicant is thus not only required to submit the patent number and the expiration date as part of its application, but is also required to describe the scope of the patent and relate the drug substance, drug product, or method of use in question to the particular patent. Furthermore, the regulation requires an NDA holder or applicant to complete FDA Form 3542, which requires the applicant to identify whether the submitted patent claims a "drug substance," "drug product," or "method of use," and link such information to each patent for which information is being submitted. See J.A. 918- 20. The information in this form provides the basis for the Orange Book listing. See 21 C.F.R. § 314.53(c)(2)(ii).

Congress was well aware of this regulatory interpretation of "patent information" when it enacted the counterclaim provision. As Senator Schumer, one of the original sponsors of the amendment, stated, "The bill provides a *critical complement to the work the FDA has done in clarifying its regulations on patent listing*, but it goes much further." *Legislative and Regulatory Responses to the FTC Study on Barriers to Entry in the Pharmaceutical Marketplace: Hearing Before the S. Comm. on the Judiciary*, 108th Cong. 19 (2003) (emphasis added). Additionally, in several places in the legislative history the FDA regulation is cited approvingly. See 149 Cong. Rec. S8690 (daily ed. June 26, 2003) (statement of Sen. Hatch, then-chairman of the Senate Committee on the Judiciary); 149 Cong. Rec. S8197 (daily ed. June 19, 2003) (statement of Sen. Frist, then Senate Majority Leader).

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in paragraph (c)(2) of this section for each patent that meets the requirements described in paragraph (b) of this section."

Quite apart from *Chevron*, it is well established that where, as here, Congress was specifically aware of the agency's interpretation of a statutory term at the time the statute was enacted, this is compelling evidence of legislative adoption of the agency's interpretation. This principle has been recognized by the Supreme Court for decades, both in the context of reenactment of existing statutes where statutory terminology had been construed by the agency before the reenactment,[11] and in the context of new legislation utilizing terminology that the agency had previously construed.[12] Here, Congress utilized the FDA's interpretation of "patent information" by enacting the Gregg-Schumer Bill with full awareness of the agency's interpretation of the term, and the FDA's

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[11] See *United States* v. *Bd. of Comm'rs of Sheffield, Ala.*, 435 U.S. 110, 131-35 (1978) (adopting the Attorney General's interpretation of "state[s] and political subdivision" to include all political units in a designated jurisdiction where Congress was aware of the Attorney General's interpretation when it reenacted the Voting Rights Act without change in 1975); *Commarano* v. *United States*, 358 U.S. 498, 510 (1959) (adopting IRS' construction of "ordinary and necessary" business expenses as excluding sums spent to persuade the public of the desirability of proposed legislation affecting the taxpayer's business, as Congress reenacted the Internal Revenue Code without substantive change to the business expense deduction); *Hartley* v. *Comm'r*, 295 U.S. 216, 220 (1935) (adopting IRS' construction of "basis" for the purposes of a decedent's estate to be the property's value at the time of decedent's death, as Congress reenacted the pertinent Internal Revenue Code provisions without substantive change).

[12] See *Traynor* v. *Turnage*, 485 U.S. 535, 546 (1988) (adopting Veterans' Administration's construction of "willful misconduct" as including alcoholism, where Congress enacted GI Bill using the same "willful misconduct" language previously construed by the Veterans' Administration).

interpretation is binding on us in construing the statute.

Third, the legislative history makes clear that Congress was concerned with correcting Orange Book information generally. The legislative history suggests a broad concern with preventing brand manufacturers from manipulating the patent listing system in the Orange Book in order to delay entry of generics into the market. See 149 Cong. Rec. 31,200 (2003) (statement of Sen. Schumer) ("The [new] provisions close loopholes in the law and end the abusive practices in the pharmaceutical industry which have kept lower-priced generics off the market and cost consumers billions of dollars.").[13] The purpose of the statutory provision as reflected in the legislative history refers broadly to correction of Orange Book information, not just to correction of patent numbers and expiration dates. As Senator Schumer described it, "[T]he provisions enforce *the patent listing requirements at the FDA* by allowing a generic applicant, when it has been sued for patent infringement, to file a counterclaim to have the brand drug company *delist the patent* or *correct the patent information in the FDA's Orange Book*." 149 Cong. Rec. S15,746 (daily ed. Nov. 24, 2003) (emphases added).

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[13] See also 149 Cong. Rec. at S8191 (daily ed. June 19, 2003) (statement of Sen. Schumer) ("A lot of blockbuster drugs were on the market. Their patents were about to expire. The drug industry . . . came to the conclusion that they had to do everything they could, they had to pull out all the stops to extend their monopolies. They came up with wild and crazy schemes to do it, such as patenting the substance the body makes when the drug is ingested; developing computer programs and listing the patents on the drug; and, in one case, absurdly, a new patent was asked for because the color of the bottle was changed. That was never the concept of Hatch-Waxman.").

Under the circumstances, it seems to me that we must interpret the phrase "patent information submitted . . . under subsection (b) or (c)" to include Orange Book information that describes the scope of the patent and relates the patent number and expiration date to the drug or method of use and, in particular, that "patent information" submitted under subsections (b) and (c) must be interpreted to include the patent information required by the 2003 regulation, including method of use information.

III.

In my view, the majority also errs by interpreting "an approved method of using the drug" in 21 U.S.C. § 355(j)(5)(C)(ii)(I)(bb) to mean "any" approved method of use approved in the patentee's NDA. The majority's approach here is fundamentally inconsistent with the Supreme Court's admonition, in a recent opinion by Justice Scalia, that "[u]ltimately context determines meaning," *Johnson* v. *United States*, No. 08-6925, slip op. at 5 (U.S. Mar. 2, 2010), and the Court's repeated instruction that "[i]n expounding a statute, we must not be guided by a single sentence or member of a sentence, but look to the provisions of the whole law, and to its object and policy," *U.S. Nat'l Bank of Or.* v. *Indep. Ins. Agents of Am., Inc.*, 508 U.S. 439, 455 (1993) (quoting *United States* v. *Heirs of Boisdoré*, 49 U.S. (8 How.) 113, 122 (1849)).

The evident purpose of the counterclaim provision is to allow for the correction of "patent information submitted . . . under (b) or (c)." In other words, as discussed above, the provision is designed to provide for correction of erroneous Orange Book information submitted by the NDA applicant or holder, including information with respect to patent coverage of both

drugs and methods of use. That purpose is reflected in the language of the statute, which allows an ANDA applicant defending against an infringement action to "assert a counterclaim seeking an order requiring the [NDA] holder *to correct or delete the patent information submitted by the holder* under subsection (b) or (c) of this section *on the ground that the patent does not claim either— (aa) the drug for which the application was approved; or (bb) an approved method of using the drug*." 21 U.S.C. § 355(j)(5)(C)(ii)(I) (emphases added). In other words, if the submitted Orange Book information claims patent coverage for an approved drug not covered by the patent or a method of use not covered by the patent, that information may be corrected.

Thus, the reference to "an approved method of using the drug" in subsection (bb) must refer to *information in the Orange Book* concerning "an approved method of using the drug." The majority's error lies in focusing on the relationship between the patent and the NDA (which is not Orange Book information), rather than the relationship between the patent and the Orange Book listing. Under the majority's view, no correction of erroneous Orange Book information is permitted so long as the patent covered any approved method of use covered by the NDA. The patent can be listed in the Orange Book as erroneously covering approved use A, despite the fact that the patent actually covers approved use B, and the counterclaim provision provides no mechanism for correction. This cannot be what Congress intended.[14]

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[14] The majority suggests that Congress borrowed the statutory language from our decision in *Mylan* and that this shows that "an" means "any," because in *Mylan* the patent did not relate to

Moreover, the statutory language referring to "an approved method of using the drug" obviously refers, once again, to the terminology used in the 2003 Patent Listing Rule. That regulation required that for "each method of use patent" the NDA applicant submit certain information, including "[w]hether the patent claims one or more approved methods of using the approved drug product and a description of *each approved method of use or indication and related patent claim of the patent being submitted.*" 21 C.F.R. § 314.53(c)(2)(ii)(P)(1) (emphasis added). In other words, the regulation requires the patentee to relate the patent to the approved method of use. Subsection (bb) is directly concerned with correction of the Orange Book patent information relating the patent to the approved method of use.

Once the overall operation of the statutory scheme is understood, the text is clear. *Webster's Third New International Dictionary* describes "a" as being "used as a function word before a singular noun followed by a restrictive clause or other identifying modifier *<a man who was here yesterday>*." *Webster's Third New International Dictionary* 1 (2002) (emphasis added). This definition appears *before* the definition of "a" as "any." See *id.* As the example illustrates, "an" in this case may be the function word before the singular noun ("approved method of using the drug") conveying a particular identity through the use of a restrictive clause. The restrictive clause here is implicit—"an approved method of using the drug" logically refers to an approved method of use listed by the NDA

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any approved use. Majority Op. at 11. I have demonstrated above that Congress could not have intended to limit the counterclaim provision to the particular facts in Mylan.

holder in the Orange Book, as associated with the listed patent. Thus, "an" refers to a particular method of using the drug, that is, the particular approved method listed by the NDA holder in the Orange Book. This is the only interpretation of the statutory language that yields a result that is not plainly at variance with the purpose of the legislation as a whole. See *Nixon* v. *Mo. Mun. League*, 541 U.S. 125, 138 (2004) (citing *United States* v. *Am. Trucking Ass'n*, 310 U.S. 534, 543 (1940)). "As in all cases of statutory construction, our task is to interpret the words of these statutes in light of the purposes Congress sought to serve." *Chapman* v. *Houston Welfare Rights Org.*, 441 U.S. 600, 608 (1979).

In short, the statute must be construed to read as follows:

(ii) Counterclaim to infringement action.—

(I) In general.—If an owner of the patent or the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) of this section on the ground that the patent does not claim either—

(aa) the [associated] drug for which the application was approved;

or

(bb) an [associated] approved method of using the drug.

An error in an Orange Book use code, which covers an unpatented method of use, is subject to correction under a proper reading of the counterclaim provision.

IV.

The facts in this case well illustrate the true manipulation that the counterclaim provision was designed to avoid. Here Novo Nordisk ("Novo") was originally the owner of the patent on the chemical composition of repaglinide, U.S. Patent No. RE37,035 ("the '035 patent"), which expired on March 14, 2009. See *Novo Nordisk A/S* v. *Caraco Pharm. Labs., Ltd.*, 656 F. Supp. 2d 729, 730 (E.D. Mich. 2009). Novo is also the owner of a patent covering the use of repaglinide in monotherapy to treat diabetes, U.S. Patent No. 5,312,924 ("the '924 patent"), which expired in September of 2006. The expiration of these patents meant that Novo could not claim any patent protection for monotherapy use of PRANDIN. However, Novo acquired an additional patent in 2004 (the patent in suit) claiming 1) a chemical composition of repaglinide and metformin; and 2) a method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient repaglinide in combination with metformin. See U.S. Patent No. 6,677,358 col.10 ll.42-43, 48-51 ("the '358 patent"). The '358 patent is not set to expire until June 12, 2018.

Following issuance of the '358 patent on January 13, 2004, Novo submitted an FDA Form 3546, dated February 5, 2004, associated with NDA 020741 (for PRANDIN). *Novo Nordisk A/S* v. *Caraco Pharm. Labs., Ltd.*, 649 F. Supp. 2d 661, 663 (E.D. Mich.

2009). The use code narrative was limited to claiming a use of PRANDIN in combination therapy. It read: "U-546—USE OF REPAGLINIDE IN COMBINATION WITH METFORMIN TO LOWER BLOOD GLUCOSE." *Id.* at 664. Thus, the Orange Book entry in 2004 included the following:

APPL/ PROD NUMBER	INGREDIENT NAME; TRADE NAME	PATENT NUMBER	PATENT /PED EXCL EXPIRES	PATENT CODE(S)
020741 001	REPAGLINIDE; PRANDIN	6677358	JUN 12, 2018	DS DP U546
020741 002	REPAGLINIDE; PRANDIN	6677358	JUN 12, 2018	DS DP U546
020741 003	REPAGLINIDE; PRANDIN	6677358	JUN 12, 2018	DS DP U546

See J.A. 1235.

Caraco Pharmaceutical Laboratories, Limited ("Caraco") filed an ANDA seeking approval to market repaglinide for the treatment of diabetes in anticipation of the expiration of the '035 patent. *Novo Nordisk*, 649 F. Supp. 2d at 662. In June 2005, Novo sued Caraco, claiming that if Caraco marketed repaglinide, it would infringe. Complaint at 3, *Novo Nordisk*, 649 F. Supp. 2d 661 (No. 05-cv-40188).[15] Novo did not claim that Caraco would infringe the '924 patent or the '035 patent; nor could Novo make such a claim

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[15] In particular, Novo asserted that marketing of repaglinide would infringe claim 4 of the '358 patent, which claimed:

> A method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin.

'358 patent col. 10 ll.48-51.

since Caraco sought approval to market repaglinide only after both patents expired. Rather, Novo claimed that Caraco would induce infringement of the '358 patent, apparently because the Caraco label would suggest the use of repaglinide together with metformin.

Following the FDA's suggestion, Caraco sought a section viii certification, making clear that it was not seeking approval to market the use of repaglinide in combination with metformin (by limiting its label to the monotherapy use).[16] Based on the existing U-546 use code description for PRANDIN (limiting the description of the patent to combination therapy), the FDA permitted Caraco to move forward with its label carving out information pertaining to use of repaglinide in combination with metformin. See J.A. 625-43.

Several months later, Novo then broadened the use code for PRANDIN associated with the '358 patent, changing the use code to read: "U-968—A METHOD FOR IMPROVING GLYCEMIC CONTROL IN ADULTS WITH TYPE 2 DIABETES MELLITUS." *Novo Nordisk*, 649 F. Supp. 2d at 664. The Orange Book listing for PRANDIN then included the following:

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[16] Caraco initially made a paragraph IV certification with respect to Claim 4 of the '358 patent and a paragraph III certification with respect to the '035 patent on repaglinide. Opposition to Plaintiffs-Appellants' Emergency Motion to Stay Mandatory Injunction Pending Appeal at exh. 7, at 3, *Novo Nordisk A/S* v. *Caraco Pharm. Labs., Ltd.*, No. 2010-1001 (Fed. Cir. Oct. 7, 2009). However, at the FDA's urging it sought a "split certification," a paragraph IV certification as to the drug product claims of the '358 patent, and a section viii certification as to the method claim. See J.A. 635.

APPL/PROD NO	PATENT NO	PATENT EXPIRATION DATE	PATENT CODES
REPAGLINIDE	PRANDIN		
N020741 001	6677358	Jun 12, 2018	DS DP U-968
N020741 002	6677358	Jun 12, 2018	DS DP U-968
N020741 003	6677358	Jun 12, 2018	DS DP U-968

See U.S. Dep't of Health & Human Servs., *Approved Drug Products with Therapeutic Equivalence Evaluations* add. A, at 157 (30th ed. 2010). Since U-968 appeared to encompass the use of repaglinide in monotherapy to treat diabetes, the FDA reversed itself and rejected Caraco's proposed labeling carve-out, requiring Caraco to include the information regarding the patented repaglinide-metformin combination therapy in its generic label.[17]

Novo acknowledges that monotherapeutic use of repaglinide is not covered by the '358 patent. See, *e.g.*, Majority Op. at 9 ("Novo and Caraco agree that the '358 patent claims only one of the three approved methods of using PRANDIN (i.e., repaglinide in combination with metformin)."). But the use code claims

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[17] With the exception of the carve-out to avoid the infringing use, the language of the generic label must otherwise match that of the original drug label. See 21 U.S.C. § 355(j)(2)(A)(v), (j)(4)(G); 21 C.F.R. § 314.94(a)(8)(iv). Thus, in this case, without the section viii carve-out, Caraco would be required to include information regarding the combination therapy included in PRANDIN's label (in the "Dosage and Administration" and "Clinical Pharmacology" sections) in its own label. See J.A. 637. The inclusion of information regarding the combination therapy would likely cause Caraco to induce infringement of the '358 patent.

that the patent does cover the monotherapy use. In my view, this is precisely the type of situation that Congress intended the counterclaim provision to address.

The concurrence blames the FDA for Caraco's predicament, adopting Novo's disingenuous argument that the FDA, and not Novo, was responsible for the change in the use code. The concurrence accuses the FDA of "gumm[ing] up the works. By requiring a single broad indication for repaglinide as part of the approved labeling, FDA created a situation where Caraco can no longer assert that its proposed labeling does not infringe the '358 patent." Concurring Op. at 2. First, the FDA did not require a change in the use code. The FDA does not interpret patents or police the Orange Book listings, the very source of the problem that led to the counterclaim provision. The FDA role in administering the Orange Book is ministerial: it simply lists the patent information that it receives from brand manufacturers, expecting those parties to abide by the statutory and regulatory mandates. See *Apotex, Inc.* v. *Thompson*, 347 F.3d 1335, 1349 (Fed. Cir. 2003) (upholding the FDA's position that the FDA's duties with respect to the Orange Book are ministerial and that the Hatch-Waxman Act does not require the FDA to police the Orange Book listings to ensure compliance with regulatory and statutory requirements).

Second, while the FDA did require a general change in oral diabetes drug labeling in November of 2007 that required a corresponding change in the PRANDIN label, there is absolutely nothing in the statute or regulations that required Novo to change

the use code to track this new indication.[18] The FDA did not direct or request that Novo change its use code to reflect the new indication, nor was Novo required under FDA regulations to make such a change. Indeed, in response to questioning at oral argument, Novo admitted this. Oral Arg. at 1:40-1:46 ([The FDA directive of 2007] did not require [a change in the use code] . . .").

However, Novo argues that the labeling change required by the FDA in the "Indication" part of the label made the use code change appropriate. Novo argues that FDA Form 3542 allows them to submit either the method of use or the indication for the use code. Appellant's Br. 36 ("FDA's guidance is expressly written in the alternative: An applicant may describe *either* the indication or the method of use."). That is partially correct,[19] but the form also requires that the use code information refer to that portion of the label that relates to a patented use. See J.A. 919. An approved label, as in this case, may cover both patented uses and unpatented uses. Nothing in the FDA regulations or FDA Form 3542 suggests that the patentee may derive Orange Book use code information from that portion of the label referring to *unpatented* uses. Quite the contrary, the applicable regulations and

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[18] In November of 2007, as part of an ongoing reevaluation of the professional labeling of all oral antidiabetic drugs, the FDA required Novo to replace all separate indications with the following sentence: "PRANDIN is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus." See J.A. 667-68.

[19] The form provides alternatives with respect to submission of a proposed use code—it directs the NDA holder to "provide the information on the indication or method of use for the Orange Book." J.A. 920.

FDA Form 3542 are clear that the patentee is required to utilize those portions of the label that refer to the *patented use*. See 21 C.F.R. § 314.53(c)(2)(ii)(P)(2) (requiring the NDA holder to identify "the specific section of the approved labeling for the drug product that corresponds to the method of use claimed by the patent submitted"); J.A. 919.

Here, the patentee did exactly what was expressly forbidden. For the proposed use code description submitted on the FDA Form 3542, Novo submitted the following: "A method for improving glycemic control in adults with type 2 diabetes mellitus." J.A. 673. It thus utilized that portion of PRANDIN's label that refers to the use of repaglinide standing alone to treat diabetes (an unpatented use), not to the use of repaglinide together with metformin (a patented use).[20] There is no justification for using a portion of the label referring to an unpatented use to describe a patented use.

The manipulative nature of Novo's actions is confirmed not only by the lack of justification for the change, but also by the timing of the change (two years after the labeling change was initiated by the FDA and immediately after the FDA approved Caraco's section viii carve-out), and by its own admission that preventing approval of Caraco's ANDA was part of the motivation for changing the use code. At oral argument, Novo conceded that the decision to change the use code was in part "a response to the section viii ruling . . . in December '08 from FDA." Oral Arg. at 3:43-4:03.

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[20] Various other parts of the current PRANDIN label reference the combination therapy, such as the "Clinical Pharmacology" and "Dosage and Administration" sections of the label.

V.

Finally, the majority opinion suggests that the court's restrictive interpretation of the counterclaim provision is not so bad because it does not leave Caraco without a remedy to correct the erroneous Orange Book listing. The majority is sanguine about the outcome, believing that forcing Caraco to defend the paragraph IV infringement suit will "facilitate[] efficient resolution of disputes concerning potential overlapping of protected and unprotected uses." Majority Op. at 12. In contrast, the concurrence doubts that there is a remedy in the infringement suit, and I agree. As the concurrence notes, "[b]y requiring a single broad indication for repaglinide as part of the approved labeling, FDA created a situation where Caraco can no longer assert that its proposed labeling does not infringe the '358 patent." Concurring Op. at 2. Indeed, Novo's adoption of a broad use code for PRANDIN likely prevents Caraco from being able to disprove infringement in the paragraph IV lawsuit, because Caraco is now compelled to include information regarding the patented combination therapy in its label.

Nor would there be a remedy in a suit under the Administrative Procedure Act ("APA"). To be sure, we have held that an APA action could be brought to challenge FDA action in refusing to police use codes in the Orange Book, but at the same time we expressed no view as to whether such an action would succeed. See *Andrx Pharms., Inc.* v. *Biovail Corp.*, 276 F.3d 1368, 1379 (Fed. Cir. 2002). To succeed in such an action, the ANDA applicant would have to establish that the FDA's refusal to police use codes was arbitrary and capricious, or contrary to the statute. 5 U.S.C. § 706(2)(A). We have subsequently held

that the FDA is under no statutory obligation to determine the correctness of particular patent listings in the Orange Book, and that nothing in the Hatch-Waxman Act requires the FDA to screen Orange Book submissions by NDA applicants and refuse those that do not satisfy the statutory requirements for listing. See *Apotex*, 347 F.3d at 1349; see also *aaiPharma Inc.* v. *Thompson*, 296 F.3d 227, 238-40 (4th Cir. 2002). Moreover, the very enactment of the counterclaim provision assumed that no alternative remedy was available to an ANDA applicant challenging an Orange Book listing. Today's decision strikingly limits the counterclaim provision with the consequence that, in all likelihood, the ANDA applicant is left without any remedy to correct an erroneous Orange Book listing with respect to a method of use patent. This cannot be what Congress intended.

* * *

In summary, the majority's crabbed view of the statute sanctions an unjustified manipulation of the Orange Book. In this suit, Caraco seeks to compel Novo to correct the use code for PRANDIN, and to reinstate the earlier U-546 use code describing the '358 patent as covering the "USE OF REPAGLINIDE IN COMBINATION WITH METFORMIN TO LOWER BLOOD GLUCOSE." Under the correct construction of the counterclaim provision, the district court properly held that Caraco was entitled to an order reinstating the former U-546 use code. See *Novo Nordisk*, 656 F. Supp. 2d 729.

In holding that the counterclaim provision is unavailable, the majority's approach is notably inconsistent with the approach adopted by our sister circuit in another recent Hatch-Waxman Act case, *Teva*

Pharmaceuticals USA, Inc. v. *Sebelius*, 595 F.3d 1303 (D.C. Cir. 2010). There the court construed another provision of the 2003 amendments concerning the NDA holder's withdrawal of "patent information submitted under subsection (b) or (c)." 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)(CC). The statute provided that if such information were "withdrawn by the holder of the application," the period of exclusivity of the ANDA first filer would be forfeited. See *id.* The court held that only the withdrawal resulting from a successful counterclaim suit triggered a forfeiture and not a voluntary withdrawal. *Teva*, 595 F.3d at 1317. This was so because there was "*not a single cogent reason* why Congress might have permitted brand manufacturers to trigger subsection (CC) by withdrawing a challenged patent, outside the counterclaim scenario," *id.* (emphasis in original), and because of the strong policy of the statute favoring the 180-day marketing exclusivity period. *Id.* at 1318. Here the majority reaches a result that is unsupported by any cogent reason for leaving an ANDA applicant without a remedy to correct an erroneous Orange Book listing with respect to a method of use patent, and is directly contrary to the congressional purpose. I respectfully dissent.

APPENDIX B

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

NOVO NORDISK A/S AND NOVO NORDISK, INC.,
Plaintiffs-Appellants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD.,
AND SUN PHARMACEUTICAL INDUSTRIES, LTD.
Defendants-Appellees

2010-1001

Appeal from the United States District Court for the Eastern District of Michigan in case no. 2:05-CV-40188, Judge Avern Cohn.

ON PETITION FOR PANEL REHEARING AND REHEARING EN BANC

Before RADER, Chief Judge,* NEWMAN, CLEVENGER,** LOURIE, BRYSON, GAJARSA, LINN, DYK, PROST, and MOORE, Circuit Judges.

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* Randall R. Rader assumed the position of Chief Judge on June 1, 2010.

** Raymond C. Clevenger, III took part in the decision on the panel rehearing.

PER CURIAM.

GAJARSA, Circuit Judge, with whom DYK, Circuit Judge, joins, dissents from the denial of the petition for rehearing en banc.

JAMES F. HURST, Winston & Strawn LLP, of Chicago, Illinois, filed a combined petition for panel hearing and rehearing en banc for defendants-appellees. With him on the petition were CHARLES B. KLEIN, STEFFEN N. JOHNSON, SCOTT H. BLACKMAN, and ANDREW C. NICHOLS, of Washington, DC; DAVID S. BLOCH, of San Francisco, California.

JOSH A. KREVITT, Gibson, Dunn & Crutcher LLP, of New York, New York, filed a response to the petition for plaintiffs-appellants. With him on the response were MARK A. PERRY, of Washington, DC; WAYNE BARSKY, of Los Angeles, California; and MICHAEL A. SITZMAN, of San Francisco, California.

WILLIAM A. RAKOCZY, Rakoczy Molino Mazzochi Siwik LLP, of Chicago, Illinois, for amicus curiae Generic Pharmaceutical Association.

SHASHANK UPADHYE, Apotex, Inc., of Toronto, ON Canada, for amicus curiae Apotex, Inc. With him on the brief was MICHAEL A. BERTA, Wilson Sonsini Goodrich & Rosati, of San Francisco, California, for Impax Laboratories, Inc.

DAVID A. BALTO, The Law Offices of David A. Balto, of Washington, DC, for amici curiae Consumer Federation of America and National Legislative Association on Prescription Drug Prices.

SHANNON M. BLOODWORTH, Perkins Coie LLP, of Washington, DC, for amicus curiae Mylan Pharmaceuticals Inc.

MICHAEL D. SHUMSKY, Kirkland & Ellis LLP, of Washington, DC for amicus curiae Teva Pharmaceuticals USA, Inc.

ORDER

Defendants-Appellees Caraco Pharmaceutical Laboratories, Ltd. and Sun Pharmaceutical Industries, Ltd. ("Caraco and Sun") filed a combined petition for panel rehearing and rehearing en banc. The panel invited a response from Plaintiffs-Appellants Novo Nordisk A/S and Novo Nordisk, Inc. The court granted leave to file briefs amici curiae to Teva Pharmaceuticals, USA, Inc., Mylan Pharmaceuticals Inc., Apotex Inc. and Impax Laboratories, Inc., Consumer Federation of America and National Legislative Association on Prescription Drug Prices, and Generic Pharmaceutical Association.

The petition for rehearing was considered by the panel that heard the appeal, and thereafter the petition for rehearing en banc, the response to the petition, and briefs amici curiae were referred to the circuit judges who are authorized to request a poll on whether to rehear the appeal en banc. A poll was requested, taken, and failed.

Upon consideration thereof,

IT IS ORDERED THAT:

(1) The petition of Defendants-Appellees Caraco and Sun for panel rehearing is denied.

(2) The petition of Defendants-Appellees Caraco and Sun for rehearing en banc is denied.

(3) The mandate of the court will issue on August 5, 2010.

July 29, 2010

FOR THE COURT

Jan Horbaly Clerk

/s/ Jan Horbaly

cc: Josh A. Krevitt, Esq.
James F. Hurst, Esq.
William A. Rakoczy, Esq.
Michael D. Shumsky, Esq.
Shannon M. Bloodworth, Esq.
Shashank Upadhye, Esq.
Michael A. Berta, Esq.
David A. Balto, Esq.

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

NOVO NORDISK A/S AND NOVO NORDISK, INC.,
Plaintiffs-Appellants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD.,
AND SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Appellees.

2010-1001

Appeal from the U.S. District Court for the Eastern District of Michigan (2:05-CV-40188) Judge Avern Cohn.

ON PETITION FOR REHEARING EN BANC

GAJARSA, Circuit Judge, with whom DYK, Circuit Judge, joins, dissenting from the denial of the petition for rehearing en banc.

This case involves the statutory construction of 21 U.S.C. § 355(j)(5)(C)(ii) ("counterclaim provision"), a critical provision of the Hatch-Waxman Act ("HWA") that has not previously been construed.[1] In 2003,

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[1] The counterclaim provision provides:
(ii) Counterclaim to infringement action

Congress enacted the counterclaim provision in order to prevent patent holders from making unwarranted or inaccurate claims of patent coverage in the Orange Book.[2] Patent holders previously made such claims in order to delay the onset of competition from generic drug manufacturers, by preventing or delaying FDA approval of a generic manufacturer's Abbreviated New Drug Application ("ANDA").[3] In *Mylan Pharmaceuticals, Inc. v. Thompson*, 268 F.3d 1323 (Fed. Cir. 2001), this court held that generic drug manufacturers could not sue to correct inaccurate and expansive Orange Book listings, thus inspiring Congress to amend the HWA to include the counterclaim provision. The majority's opinion

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(I) In general

If an owner of the patent or the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) of this section on the ground that the patent does not claim either--

(aa) the drug for which the application was approved; or

(bb) an approved method of using the drug.

[2] Under the HWA, Congress required the Food and Drug Administration ("FDA") to maintain and publish a list of patents associated with approved drugs and methods of use. See 21 U.S.C. § 355(b)(1) (2006). The Orange Book, or the Approved Drug Products with Therapeutic Equivalence Evaluations, implements this statutory mandate. See 21 C.F.R. § 314.53(c)(2)(i)(O).

[3] A generic manufacturer may piggyback on the safety and efficacy data the original drug manufacturer submitted in its "New Drug Application" ("NDA"), and may seek approval for an identical method of use for its identical generic product by submitting an ANDA. See 21 U.S.C. § 355(j).

construes the counterclaim provision contrary to its manifest Congressional purpose. That construction renders 21 U.S.C. § 355(j)(2)(A)(viii) ("Section viii") carve-out statements a virtual nullity and leaves generic drug manufacturers without a remedy to challenge inaccurate Orange Book listings with respect to method of use patents. Therefore, I respectfully dissent from the court's denial of Caraco's petition for rehearing en banc.

The background and facts of this case are well laid out in Judge Dyk's dissent in the original panel decision. See *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 601 F.3d 1359, 1370-78 (Fed. Cir. 2010) (Dyk, J., dissenting). As the dissent explains, the majority's opinion adopts an overly narrow construction of "patent information" and an overly broad construction of "an approved method of using the drug." See *id.* at 1370-72, 1376-78. Both constructions are irreconcilable with pre-existing FDA regulations, the text of the HWA, and Congressional intent. See *id.* at 1370-78. I believe rehearing the case en banc is necessary to rectify these improper constructions.

Not only is the majority's construction of the counterclaim provision erroneous, it also eliminates the careful balance Congress has struck between encouraging pharmaceutical discoveries and ensuring that the American people have access to low cost generic drugs. Specifically, the majority's opinion seriously undermines Section viii, a critical provision of the HWA that facilitates the approval and marketing of lower-cost generic drugs for uses no longer protected by a patent.

Under the HWA, Section viii comes into play when a patent listed in the Orange Book "claims one, but not all, approved methods of using a drug." Id. at 1365. Section viii permits a generic manufacturer seeking to market an approved use of a drug to certify that its method of using the drug (as described on its label) is not covered by a patent in the Orange Book. Normally, the label associated with the generic version of a drug must be exactly the same as the label associated with the drug approved in the original New Drug Application. 21 U.S.C. § 355(j)(2)(A)(v), (j)(4)(G); 21 C.F.R. § 14.94(a)(8)(iv). A Section viii statement allows a generic manufacturer to avoid infringement by deleting patented used from its proposed label information, thus allowing it to avoid infringement. 21 U.S.C. § 355(j)(2)(A)(viii).

Congress intended Section viii to facilitate the approval and marketing of lower-cost generic drugs, while still respecting the patent rights of pioneering drug manufacturers. Pioneering drug manufacturers, however, have found another way to game the system by subverting Section viii carve-out statements and delaying the onset of generic competition by submitting overbroad and inaccurate use codes. Use codes are codes created by patent holders in Orange Book listings to identify the scope of their Orange Book patents. The FDA will not approve a generic manufacturer's Section viii proposed label amendment if a use code covers the proposed label. Importantly, the FDA makes no effort to determine the accuracy of use codes.[4]

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[4] The FDA has maintained, and we have affirmed, that its role in listing patents in the Orange Book is "ministerial"; it simply lists the patent information that it receives from brand manufacturers, expecting those parties to properly abide by the

In this case, Novo Nordisk (the brand drug manufacturer) owns a patent on the chemical composition of repaglinide, which expired on March 14, 2009. See U.S. Patent No. RE 37,035 ('the '035 patent). Novo also owns a patent on the use of repaglinide in combination with metformin to treat diabetes, which does not expire until 2018. See U.S. Patent No. 6,677,358 ("the '358 patent"). In addition to its combination with metformin to treat diabetes, the FDA had approved repaglinide for two other uses: (1) by itself, i.e. monotherapy and (2) in combination with thiazolidinediones. See *Novo Nordisk*, 601 F.3d at 1362. Novo does not own any patents covering the latter two approved uses.

In anticipation of the '035 patent's expiration, Caraco, the generic manufacturer, sought to market the mono- therapy use of repaglinide to treat diabetes, a use no longer covered by a patent. In June 2005, Novo sued Caraco, claiming that if Caraco marketed repaglinide, it would nonetheless infringe the '358 patent because Caraco's label would suggest the use of repaglinide together with metformin. Following the FDA's suggestion, Caraco sought a Section viii carve-out statement, making clear that it was not seeking approval to market the use of repaglinide in combination with metformin and limiting its label to the monotherapy use.

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statutory and regulatory mandates. See Apotex, Inc. v. Thompson, 347 F.3d 1335, 1349 (Fed. Cir. 2003); Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying that a Patent Claiming a Drug Is Invalid or Will Not Be Infringed, 68 Fed. Reg. 36,676, 36,683 (June 18, 2003) (codified at 21 C.F.R. pt. 314).

To defeat this Section viii carve-out statement, Novo changed the Orange Book use code associated with the '358 patent from "use of repaglinide in combination with metformin to lower blood glucose" to "a method for improving glycemic control in adults with type 2 diabetes mellitus." See *id.* at 1362-63. The latter use code unmistakably covering both patented and unpatented uses. Because the FDA declined to police this inaccurate listing, Caraco asserted the counterclaim provision in the underlying HWA litigation and requested that Novo revise its use code to reflect the '358 patent's true scope.[5] The majority opinion, however, held that counterclaim relief is not available because the '358 patent covered at least one approved use. See *id.* at 1364-65. This effectively allows a patent holder to extend its monopoly to unpatented uses.

The majority opinion thus eviscerates Section viii. A generic, like Caraco, cannot use Section viii if the pioneering manufacturer's use code is erroneously broad. With the majority's blessing, pioneering drug manufacturers now have every incentive to follow Novo's lead and draft exceedingly broad use codes thereby insulating themselves from generic competition and rendering Section viii a dead letter.

The evisceration of Section viii is exacerbated by the fact that, as Judge Clevenger points out in his concurring opinion in the panel decision, the majority

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[5] Novo argued, and the majority and concurrence agreed, that this predicament was somehow the fault of the FDA, which had required Novo (and all oral diabetes drug manufacturers) to change the "Indications" part of the drug label for therapeutic reasons. As explained in the dissenting opinion, Novo admits that the FDA did not require Novo's inaccurate listing. Novo Nordisk, 601 F.3d at 1380 (Dyk, J. dissenting).

decision likely leaves generic manufacturers such as Caraco with no other remedy. See *Novo Nordisk*, 601 F.3d at 1367-68 (Clevenger, J., concurring). The FDA declined to grant Caraco's Section viii carve-out because the broad use code for the '358 patent now appears to cover Caraco's proposed carve-out label. Caraco also cannot disprove infringement in the infringement lawsuit because the FDA requires it to use Novo's original label, which includes information regarding the patented combination therapy. Thus, Caraco will apparently have to wait to launch its generic repaglinide product until 2018, the date on which Novo's '358 patent on the combination therapy expires— despite the fact that the '358 patent *concededly does not cover the use for which Caraco seeks to market the drug*. This is an untenable and absurd result, and contravenes the intent of Congress in adopting the counterclaim provision.

Finally, the majority opinion effectively invalidates the FDA's effort to define "patent information" for the purposes of the counterclaim provision. See *Novo Nordisk*, 601 F.3d at 1366-67. This invalidation is especially troubling given Congress's explicit approval of those regulations. See Legislative and Regulatory Responses to the FTC Study on Barriers to Entry in the Pharmaceutical Marketplace: Hearing Before the S. Comm. on the Judiciary, 108th Cong. 19 (2003) (Statement of Sen. Schumer) ("The bill provides a critical complement to the work the FDA has done in clarifying its regulations on patent listing, but it goes much further."). Without even requesting the views of the FDA, the majority opinion refuses to give effect to the FDA's interpretation of an important statutory term. See *Apotex, Inc. v. Thompson*, 347 F.3d 1335, 1351-52

(Fed. Cir. 2003) ("Deference is due to an administrative agency's regulations particularly when the subject matter of the regulatory authority is a highly detailed regulatory program to which the agency has brought its specialized expertise, a characterization that aptly describes the FDA's role in the context of the regulatory scheme created pursuant to the Hatch-Waxman Act." (citation and quotations omitted)).

Because the majority's statutory construction of the counterclaim provision abrogates the HWA and frustrates the clear intent of Congress, I dissent from the court's denial of Caraco's request for rehearing en banc.

APPENDIX C

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC. Plaintiffs-Counterclaim Defendants, v. CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD. Defendants-CounterclaimPlaintiffs.	Civil Action No. 2:05CV 40188 Judge Avern Cohn

ORDER AND INJUNCTION

The Court has granted Caraco's Motion for Summary Judgment on its Fourth Counterclaim and Sixth Affirmative Defense (Dkt #317), with regard to Caraco's Fourth Counterclaim asserted under 21 U.S.C. § 355(j)(5)(C)(ii)(I)(bb), as set forth in the Court's Decision re: Doc. 318 (Dkt # 421). The Court previously denied Novo Nordisk's Motion to Dismiss (Dkt #337) in a Memorandum decision (Dkt #371). In accordance with those two decisions, the Court hereby enters the following Injunction:

Novo Nordisk is hereby directed by mandatory injunction under 21 U.S.C.

§ 355(j)(5)(C)(ii)(1)(bb) to correct within twenty (20) days from the date of this Order and Injunction its inaccurate description of the '358 patent by submitting to FDA an amended Form FDA 3542 that

reinstates its former U-546 listing for Prandin and describes claim 4 of the '358 patent in section 4.2b as covering the "use of repaglinide in combination with metformin to lower blood glucose."

SO ORDERED this 25th day of September, 2009

s/Avern Cohn

AVERN COHN
United States District Judge

APPENDIX D

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

NOVO NORDISK A/S and
NOVO NORDISK, INC.,

Plaintiffs,

Case No. 05-40188
vs- Hon: AVERN COHN

CARACO PHARMACEUTICAL
LABORATORIES, LTD. and
SUN PHARMACEUTICAL INDUSTRIES, LTD.,

Defendants,

DECISION RE: DOC. 318

This is a patent case involving the drug repaglinide marketed by Novo Nordisk (Novo) under the trade name Prandin. Now before the Court is Caraco Pharmaceutical Laboratories' (Caraco) Motion for Summary Judgment on Count IV of Its Third Amended Counterclaim and Sixth Affirmative Defense for Patent Misuse (Dkt. 318). The background of the case as well as Caraco's motion is described in the Court's decisions reported at 450 F. Supp. 2d 757 (E.D. Mich. 2006) (finding allegations of complainant sufficient to state a claim against Sun) and 2009 WL 2768955 (E.D. Mich. Aug. 31, 2009) (holding that Caraco can challenge an alleged incorrect use code narrative and the Hatch-Waxman Act allows for the affirmative defense of patent misuse in such circumstances).

For the reasons which follow, the Court finds that Novo has improperly filed with the FDA for listing in the Orange Book the use code narrative for the method of use of claim 4 of the '368 patent relating to Prandin, and Caraco is entitled to a mandatory injunction requiring Novo to request the FDA to delist the U-968 listing for Prandin, and reinstate its former U-546 listing for Prandin. Novo's defense to Caraco's motion is a farrago of misstated and irrelevant facts and misstated law.

Novo's patent on repaglinide, RE37,035, expired on March 14, 2009. Caraco's ANDA covers repaglinide. The '358 patent which is the subject of this patent action does not cover repaglinide; it covers repaglinide only in combination with metformin. The U-968 use code narrative for the '358 patent states "a method for improving glycemic control in adults with type 2 diabetes mellitus." It is so broad as to incorrectly suggest that the '358 patent generically covers three (3) different FDA-approved methods of use of repaglinide:

- monotherapy treatment
- treatment in combination with thiazolidinediones
- treatment in combination with metformin

However, Novo admits that the first two (2) uses are not covered by claim 4 of the '358 patent. Caraco seeks FDA approval only to market a generic version of repaglinide; it does not seek approval to market repaglinide in combination with metformin, the only use covered by claim 4 of the '358 patent.

Novo filed the new U-968 use code on May 6, 2009, shortly after the '035 patent expired, as a

significantly broadened replacement for use code U-546 that it previously submitted for the '358 patent.[1] As a result of the revised use code, the FDA will no longer permit Caraco to file a "section viii statement" carving out the patented repaglinide-metformin combination therapy as a predicate for securing approval of Caraco's ANDA to market its generic repaglinide for non-infringing uses.

Because the FDA does not review use code narratives as explained in the August 31, 2009, decision, it has required Caraco as part of its ANDA to "submit an updated patent certification addressing the 6,677,358 patent and its associated Use Code 968." Fax from William Peter Rickman, Director of the Division of Labeling and Program Support, FDA, to Veeranna Lolla, Caraco Pharmaceutical Laboratories (Aug. 3, 2009). Caraco has therefore been seriously disadvantaged by the improper U-968 use code narrative.

Novo acknowledges that monotherapeutic use of repaglinide is not covered by the '358 patent: "[T]he '358 patent contains 5 claims one of which (claim 4) is directed to a method of treatment of NIDDM with a combination of repaglinide and metformin." Letter from Rosemarie R. Wilk-Orescan, Senior Counsel, Novo Nordisk, to the FDA (June 9, 2008).

This limitation is reiterated in the Novo's Amended Complaint: "In the '358 patent claim. . .a method for treating NIDDU by administering to a patient in need of treatment repaglinide in

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[1] U-546 specified "use of repaglinide in combination with metformin to lower blood glucose."

combination with metformin (claim 4)." Amended Complaint at ¶ 10, *Novo Nordisk* v. *Caraco Pharmaceutical Laboratories*, No. 05-40188 (E.D. Mich. Sept. 14, 2005). The Orange Book listing of Prandin reads:

Proprietary Name PRANDIN

Patent Data

Appl. No	Prod. No.	Patent No.	Patent Expiration	Patent Use Code
020741	001	6,677,358	06/12/2018	U-968[2]
020741	001	RE37,035	03/14/2009	

The FDA has made clear that a use code description must be "accurate and detailed." 68 Fed. Reg. 36,682 (June 18, 2003).

FDA regulations state that the use code must properly describe in sufficient detail the scope of the patented method covering an approved use of the referenced drug. 21 C.F.R. § 314.53(c)(2)(ii). The Patent Information submitted by Novo on its May 6, 2009 Form FDA 3542 for Prandin did not comply with the applicable FDA regulations and instructions, resulting in the U-968 use code that seriously misrepresents the approved method of use covered by claim 4. The Memorandum of August 31, 2009 summarized the clear legislative intent behind the 2003 amendments to Hatch-Waxman that added the counterclaim provision, § 355(j)(5)(C)(ii), namely, to curb Orange Book abuses arising from

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[2] Patent Use Code U-968: A method for improving glycemic control in adults with type 2 diabetes mellitus.

misinformation regarding listed patents. As provided for by the statute Caraco is entitled to "an order requiring [Novo] to correct . . . the patent information submitted" to the FDA in Form 3542. 21 U.S.C. § 355(j)(5)(C)(ii).

Caraco is correct when it says:

> Novo . . . asserts . . . that the following accurately and completely describes the scope of the '358 patent's method claim: "a method for improving glycemic control in adults with Type 2 diabetes mellitus." This new use code is . . vague on its face because it does not provide, as [the regulations] requirell, "[t]he description of the patented method of use" in a manner that is both "accurate and detailed." 21 C.F.R. §314.53(c)(2)(ii)(P); 68 Fed. Reg. at 36682. On the contrary, this. . .use code fails to identify with any specificity whatsoever the patented method and, read literally, suggests that [the '358] patent covers any method of improving glycemic control in adults with Type 2 diabetes mellitus. [One cannot] tell from this use code description alone which of the three repaglinide uses purportedly falls within the scope of the '358 patent.

Brief of Caraco Pharmaceutical Laboratories at 10, *Novo Nordisk* v. *Caraco Pharmaceutical Laboratories*, No. 05-40188 (E.D. Mich. June 19, 2009).

Lastly, Novo proposed the new use code narrative not to more accurately describe the method of use of Prandin covered by claim 4 of the '358 patent, but "as part of its longstanding efforts to ensure that information about the predominant approved use of repaglinide — i.e., in combination therapy with

metformin — is provided to repaglinide consumers." Brief of Novo Nordisk. at 25, *Novo Nordisk* v. *Caraco Pharmaceutical Laboratories*, No. 05-40188 (E.D. Mich. Sept. 10, 2009).

Novo is not a private FDA. Novo, by the change in the use code narrative is attempting to extend the life of an expired patent. The FDA is fully equipped to ensure that the label for Caraco's generic version of repaglinide is adequate to inform the public.

Caraco shall submit an order implementing this decision on notice to Novo.

Dated: September 24, 2009 s/Avern Cohn
U.S. District Court Judge

CERTIFICATE OF SERVICE

I hereby certify that a copy of the foregoing document was mailed to the attorneys of record on this date, September 24, 2009, by electronic and/or ordinary mail.

s/Julie Owens
Case Manager
(313) 234-5160

APPDENDIX E

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

NOVO NORDISK A/S and
NOVO NORDISK, INC.,

Plaintiffs,

-vs-

Case No. 05-40188
Hon: AVERN COHN

CARACO PHARMACEUTICAL
LABORATORIES, LTD. and
SUN PHARMACEUTICAL INDUSTRIES, LTD.,

Defendants.

_____/

MEMORANDUM

This memorandum explains the reasons for denying plaintiffs' motion (Doc. 337) to dismiss defendants' Count IV of the Third Amended Answer and Counterclaim (Doc. 309) (for an order requiring correction of a "use code"), and to Strike Defendants' Sixth Affirmative Defense (Doc. 309) (for an order requiring correction of a "use code") in an order entered on August 20, 2009 (Doc. 369) The order is not a decision on the merits. The order means only that the Counterclaim states a cognizable cause of action and that the Affirmative Defense states a cognizable position.

A.

This is a Hatch-Waxman[1] case, Pub. L. No. 98-417, 98 Stat. 1585 (1984), 21 USC § 355, *et seq.* Defendant, Caraco Pharmaceutical Laboratories, Ltd. (Caraco), a generic drug manufacturer, has pending before the Food and Drug Administration (FDA) an Abbreviated New Drug Application (ANDA) for repaglinide, a diabetes control drug. Repaglinide was first brought to market by plaintiffs, Novo Nordisk A/S and Novo Nordisk, Inc. (Novo), proprietary drug manufacturers, under the trade name Prandin. Novo processed the New Drug Application (NDA) for repaglinide under NDA Number 20-741, and claimed patent protection for it under U.S. Patent No. RE37,035E (the '035 patent). The '035 patent expired on March 14, 2009.

B.

In anticipation of the expiration of the '035 patent, Caraco filed an ANDA for approval to market repaglinide. After receiving notice of Caraco's ANDA, Novo sued Caraco for infringement of U.S. Patent No. 6,677,358B1 (the '358 patent) claiming that if Caraco marketed repaglinide it would contributorily infringe the '358 patent, and particularly claim 4 which reads:

> A method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin.

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1 See CONG. RES. SERV., CRS REPORT FOR CONGRESS, NO. RL 30756, PATENT LAW AND ITS APPLICATION TO THE PHARMACEUTICAL INDUSTRY: AN EXAMINATION OF THE DRUG PRICE COMPETITION AND PATENT TERM RESTORATION ACT OF 1984 ("THE HATCH-WAXMAN ACT") (UPDATED 2005).

Caraco responded by asserting that the '358 patent was invalid and unenforceable because of misconduct before the Patent Office. Caraco also asserted that its sale of repaglinide would not infringe the '358 patent.

C.

The '358 patent was intended by Novo to cover a new product, Prandimet, a combination of repaglinide with metformin. Novo filed a NDA for Prandimet which was processed by the FDA under NDA 22-386. As part of the application process Novo filed two (2) Forms FDA 3546, Patent Information Submitted Upon And After Approval Of An NDA Or Supplement.[2]2

The first FDA 3546, dated February 05, 2004, in pertinent part reads:

NDA NUMBER: NDA20-741
TRADE NAME: Prandin
ACTIVE INGREDIENT: Repaglinide
United States Patent Number: U.S. 6,677,358 B1
Patent Claim Number: 4

(Continued on next page)

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[2] Form FDA 3542 is designed to elicit the patent information called for by 21 U.S.C. § 355(b)(1)(G), 21 C.F.R. § 314.53(b)(1) and 68 Fed. Reg. 36,683. *See* Exhibit A; *see also* Orange Book preface *infra* fn 4, at 30 (Exhibit B).

If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description	Use:3[3] (Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book[4]. . . .) Use of repaglinide in combination with metformin to lower blood glucose.

The second Form FDA 3546, dated October 01, 2008, in pertinent part reads:

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[3] Form FDA 3542 instructions state in part:

4. Method of Use

4.2) For each approved use of the drug claimed by the patent, identify by number the claim(s) in the patent that claim the approved use of the drug. An applicant may list together multiple claim numbers and information for each approved method of use, if applicable. However, each approved method of use must be separately listed within this section of the form.

4.2a)Specify the part of the approved drug labeling that is claimed by the patent.

4.2b) The answer to this question will be what FDA uses to create a "use code" for Orange Book publication. The use code designates a method of use patent that claims the approved indication or use of a drug product. Each approved use claimed by the patent should be separately identified in this section and contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method of use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval. . . .

NDA NUMBER: 22-386
TRADE NAME: Prandimet (repaglinide/metformin HCI) tablets
ACTIVE INGREDIENT: repaglinide/metformin HCI
United States Patent Number: U.S. 6,677,358
Patent Claim Number: 4

If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description.	Use: (Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book. . . .) Use of repaglinide in combination with metformin to lower blood glucose.

The Use Code narrative for each of the two (2) Form 3546 reads: U-546 - USE OF REPAGLINIDE IN COMBINATION WITH METFORMIN TO LOWER BLOOD GLUCOSE.

D.

On May 06, 2009, Novo filed an amended FDA 3542, in pertinent part as follows:

NDA NUMBER: 20-741
TRADE NAME: Prandin
ACTIVE INGREDIENT: Repaglinide
United States Patent Number: U.S. 6,677,358
Patent Claim Number: 4

If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description.	Use: (Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book. . . .) A method for improving glycemic control in adults with type 2 diabetes mellitus.

As part of this filing, Novo wrote the FDA as follows:

> Re: TIME SENSITIVE PATENT INFORMATION
> NDA 20-741, Prandin® (repaglinide)
>
> To the Orange Book Staff:
>
> In accordance with Section 314.53(c) and (d) of FDA regulations, please find an original and two copies of Form FDA 3542, containing an AMENDMENT to the patent information for the above-referenced NDA. The information being submitted is to amend the use code relating to U.S. Patent No. 6,677,358 to correspond with the change in labeling required by FDA in November 28, 2007 (and to correct an unrelated inadvertent error in the original Form 3542.) This amendment is not applicable to NDA 22-386, PrandiMet® (metformin hydrochloride/repaglinide), which will retain its present use code relating to U.S. Patent No. 6,677,358.
>
> Applicant believes the use code should be changed. Therefore, please remove use code U-546 from the Orange Book for the listed drug

(Prandin) and substitute with the use code contained in this form.[4]

NDA 20-741 is the NDA number under which Novo originally processed its NDA for repaglinide under the '035 patent.

The Use Code narrative following the change reads:

> U-968-A METHOD FOR IMPROVING GLYCEMIC CONTROL IN ADULTS WITH TYPE 2 DIABETES MELLITUS.

II.

The filing of the new Form FDA 3542 by Novo on May 06, 2009, and the new Use Code, U-968 narrative for repaglinide, prompted the filing by Caraco of the Counterclaim and the Affirmative Defense, at which Novo's motion is directed, and which the Court has denied.

A.

The Counterclaim reads:

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[4] Plaintiffs' reasons for the new Form FDA 3542 were described by Novo during a hearing on July 15, 2009, as follows:

> MR. SITZMAN [Novo's counsel]: . . .the change in use code was designed to do two things. One is to make it consistent with the indication that the FDA required.
>
> The other reason that the use code was changed in May 2009 was as a result of several different things.
>
> ***
>
> . . .and two, that it would prevent Caraco from carving out of its label the most critical and vital information to this drug.

97. Under 21 USC § 355(j)(5)(C)(ii), Caraco seeks an order requiring Plaintiffs to correct the use code information submitted by plaintiffs.

98. Plaintiffs' original Prandin use code for the '358 patent was: "U-546: use of repaglinide in combination with metformin to lower blood glucose."

99. On or about May 6, 2009, Plaintiffs changed the use code for the '358 patent in reference to Prandin to one with a much broader scope: "U-968: a method for improving glycemic control in adults with Type 2 diabetes mellitus." This new use code does not purport to specifically or accurately describe the patented method of use found in claim 4 of the '358 patent, as required by FDA regulations.

100. Novo's revised use code could be read as suggesting that the '358 patent covers all approved methods of using repaglinide (including monotherapy and combination with TZDs). But the '358 patent cannot possibly be construed to cover any method of use other than "repaglinide in combination with metformin."

101. Caraco is entitled to an Order requiring Plaintiffs to correct the patent information submitted by Plaintiffs for the `358 patent's method claim on the ground that the patent does not claim the approved methods of using repaglinide as monotherapy or in combination therapy with TZDs. In particular, Plaintiffs must correct the use code for the '358 patent in reference to Prandin, submitted on or about May 6, 2009, from "U-968: a method for improving glycemic control in adults with Type 2 diabetes mellitus" to the original use code: "U-546: use of repaglinide in combination with metformin to lower blood glucose."

B.

The Affirmative Defense reads:

31. The claims of the '358 patent are unenforceable due to patent misuse.

32. Plaintiffs have misused their rights under the '358 patent, including by providing FDA with a materially inaccurate and fraudulent use code description for that patent. Plaintiffs have improperly and illegally expanded the legitimate scope of the `358 patent to delay or prevent FDA approval of Caraco's ANDA, and in this fashion also have illegally extended the life of Novo's U.S. Patent No. RE37,035, which expired on March 14, 2009.

C.

Novo takes issue with Caraco's right to file the Counterclaim and Affirmative Defense as follows:

> Caraco's Fourth Counterclaim "seeks an order requiring Plaintiffs to correct the use code information submitted" to the Food and Drug Administration ("FDA"). Third Amended Answer and Counterclaims, ¶97. Even assuming the truth of Caraco's allegation of inaccuracy, no cause of action has ever been authorized by Congress, or recognized by any court, to correct an inaccurate use code. Hatch-Waxman authorizes only two specific counterclaims by an ANDA filer for correction of the patent information submitted by an NDA holder. Caraco's Fourth Counterclaim is not even remotely within the narrow scope of either of the *two permissible counterclaims*. Hatch-Waxman expressly rules out all claims and counterclaims

"other than" the *two permissible counterclaims* (emphasis added).

Caraco's Sixth Affirmative Defense and other allegations of "patent misuse" based on the use code information submitted to the FDA should be stricken. The Federal Circuit has made clear that neither a defense to patent infringement, nor a claim of patent misuse, can be based on the propriety of the patent information submitted for inclusion in the Orange Book. *See Mylan Pharms., Inc.* v. *Thompson*, 268 F.3d 1323 (Fed. Cir. 2001); *Schwarz Pharrma, Inc.* v. *Teva Pharms. USA, Inc.*, 2005 WL 4158850 (D.N.J. Feb. 4, 2005).

The "two permissible counterclaims" according to Novo are limited to correction of

the patent number and the patent expiration date. III. A.

1.

21 U.S.C. § 355(j)(5)(C)(ii), on which Caraco relies reads in part

(ii) Counterclaim to infringement action. —

(I) In general. — If an owner of the patent or the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) of this section

on the ground that the patent does not claim either —

(aa) the drug for which the application was approved; or

(bb) an approved method of using the drug.

(II) No independent cause of action. — Subclause (I) does not authorize the assertion of a claim described in subclause (I) in any civil action or proceeding other than a counterclaim described in subclause (I).

2.

Section 355(j)(5)(C)(ii) was not part of Hatch-Waxman, Pub. L. No. 98417,[6] as initially enacted.[5] It came into the statute with enactment of the Medicare Prescription Drug Improvement and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066.

B.

The scope of a counterclaim under § 355(j)(5)(C)(ii) allows for Caraco's challenge to the Use Code U-968 narrative which comes from the Form FDA 3542 filed by Novo on May 06, 2009 *(see supra* p. 5). This conclusion is illustrated by first an analysis of the Federal Circuit's decision in *Mylan Pharmaceuticals, Inc.* v. *Thompson*, 268 F.3d 1323 (Fed. Cir. 2001), then the legislative history of § 355(j)(5)(C)(ii), and finally post-enactment commentary.

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[5] The Drug Price Competition and Patent Term Restoration Act of 1984, Title I, Abbreviated New Drug Applications, Pub. L. No. 98-417, 98 Stat. 1585, in turn was an amendment to the Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938).

1.

The Federal Circuit's decision in *Mylan* was a reversal of the district court's decision, 139 F. Supp. 2d 1 (D.D.C. 2001). In *Mylan,* a generic drug applicant brought a declaratory judgment action challenging an Orange Book Use Code narrative associated with a particular patent. The district court held that the Use Code narrative was improperly listed. The Federal Circuit, after describing the regulatory framework reversed. Novo says of *Mylan:*

> On appeal the Federal Circuit looked to the Hatch-Waxman Amendment to determine whether this created a misuse defense

It goes on to say:

> The Federal Circuit concluded that "a view of the amendment shows no explicit provisions allowing an accused infringer to defend against infringement by challenging the propriety of the Orange Book listing of the patent."

While this is a correct description of the decision in *Mylan,* it misreferences the "amendment." The reference to "amendment" is to the original 1984 enactment of Hatch- Waxman, which was an amendment to the Federal Food, Drug and Cosmetic Act. *See supra* page 9. Novo seems to ignore subsequently-enacted Pub. L. No. 108-173, which, as described, added the counterclaim provision, § 355(j)(5)(C)(ii), as an amendment to Hatch-Waxman in 2003. *Scwartz Pharma, Inc.* v. *Teva Pharmaceuticals USA, Inc.*, 2005 WL 4158850 (D.N.J. Feb. 4, 2005) is not to the contrary. There the issue was an improper use code narrative for a patent. The fact of listing the patent was not contested.

2.

In the lead up to enactment of § 355(j)(5)(C)(ii), *Mylan* was cited more than once as an example of the inability to challenge a Use Code narrative, and the need for corrective legislation.

A CRS Report stated:

> In *Mylan Pharmaceuticals, Inc.* v. *Thompson*, 268 F.3d 1323 (Fed. Cir. 2001), an ANDA applicant contended that its cause of action arose under the patent laws. The ANDA applicant observed that listing in the Orange Book was a necessary element of the patent infringement charge brought by the NDA holder. Therefore, an argument the patent should be delisted was effectively a defense to patent infringement, reasoned the ANDA applicant. As a result, the ANDA applicant concluded that it could simply rely upon the patent laws as a basis for jurisdiction in the federal courts.
>
> The Federal Circuit disagreed, however. According to the Federal Circuit, the 1984 Act did not provide a private cause of action for delisting patents from the Orange Book. Following *Mylan Pharmaceuticals, Inc.* v. *Thompson*, an ANDA applicant could not request that a patent be removed from the Orange Book merely as a defense to patent infringement.

Congressional Research Services, CRS Report for Congress, No. 31379, *The "Hatch Waxman" Act: Selected Patent Related Issues* 11 (2002).

In a Congressional Hearing, the Acting Commissioner of the Food and Drug Administration, in a prepared statement said:

> FDA does not undertake an independent review of the patents submitted by the NDA sponsor. Issues of patent claim and infringement are matters of patent law, and FDA does not have the authority as well as the resources or capability to assess whether a submitted patent claims an approved drug and whether a claim of patent infringement could reasonably be made against an unauthorized use of the patented drug. FDA has implemented the statutory patent listing provisions by informing interested parties of what patent information is to be submitted, who must submit the information, and when and where to submit the information. The statute requires FDA to publish patent information upon approval of the NDA and, therefore, the Agency's role in the patent-listing process is ministerial. The Agency relies on the NDA holder or patent owner's signed declaration stating that the patent covers an approved drug, product's formulation, composition or use. Generic and innovator firms may resolve any disputes concerning patents in private litigation.[2]
>
> [2] *Mylan* v. *Thompson*, 268 F.3d 1323 (Fed. Cir. 2001) — A generic's claim of improper listing "is not a recognized defense to patent infringement."

Examining Issues Related to Competition in the Pharmaceutical Marketplace: A Review of the FTC Report, Generic Drug Entry Prior to Patent Expiration: Hearing Before the Subcommm. on Health of the House Com. on *Energy and Commerce*, 107th Congress 32 (Oct. 9, 2002) (statement of Lester M. Crawford, Acting Commissioner, FDA).

At the same hearing, the Chairman of the Federal Trade Commission, in prepared testimony, citing *Mylan*, said:

> One of the first potential abuses the Task Force considered was the improper listing of the patents in the FDA's Orange Book. Pursuant to current policy, the FDA does not review patents presented for listing in the Orange Book to determine whether they do, in fact, claim the drug product described in the relevant NDA [fn omitted]. Instead, the FDA takes at face value the declaration of the NDA filer that the listing is appropriate. As a result, an NDA filer acting in bad faith can successfully list patents that do not satisfy the statutory listing criteria. Once listed in the Orange Book, these patents have the same power to trigger a 30-month stay of ANDA approval as any listed patent, thereby delaying generic entry and potentially costing consumers millions, or even billions, of dollars without valid cause.
>
> In January of this year, lawsuits relating to Bristol-Myers's alleged monopolization through improper listing of a patent on its brand-name drug BuSpar[38] presented the Commission with an opportunity to clarify the *Noerr* doctrine in a way that might have a significant impact on the Commission's ongoing pharmaceutical cases. Specifically, plaintiffs alleged that, through fraudulent filings with the FDA, Bristol-Myers caused that agency to list the patent in question in the Orange Book, thereby blocking generic competition with its BuSpar product, in violation of Section 2 of the Sherman Act [fn omitted].

[38] *In re Buspirone Patent Litigation/In re Buspirone Antitrust Litigation*, 185 F. Supp. 2d 363 (S.D.N.Y. 2002) (*"In re Buspirone"*). Some of the same plaintiffs previously had brought suit under the FDC Act, requesting that the court issue an order compelling Bristol-Myers to de-list the objectionable patent. Although plaintiffs prevailed at the district court level, the Federal Circuit reversed that decision, holding that the FDC Act did not provide a private right of action to compel de-listing of a patent from the Orange Book. *See Mylan Pharmaceuticals, Inc.* v. *Thompson*, 268 F.3d 1323, 1331-32 (Fed. Cir. 2001).

Id. at 41-42 (statement of Timothy J. Muris, Chairman, FTC).

3.

The legislative history of § 355(j)(5)(C)(ii) discusses the intended scope of the counterclaim-authorizing language.

a.

A CRC Report Summary states:

> The Congress is currently debating changes to the Medicare program. H.R. 1, the Medicare Prescription Drug and Modernization Act, and S. 1, the Prescription Drug and Medicare Improvements Act, as passed by each respective body on June 27, 2003, contain provisions that would amend P.L. 98-417, the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly known as the Hatch- Waxman Act). The Hatch-Waxman Act made several significant changes to the patent laws de-

> signed to encourage innovation in the pharmaceutical industry while facilitating the speedy introduction of lower-cost generic drugs. The two bills currently under consideration would address Hatch-Waxman related issues of drug patents listed in the Orange Book. . . . This report provides a thematic side-by-side comparison of the proposed changes contained in H.R. 1 and S. 1 that would affect the Hatch-Waxman legislation.

Congressional Research Services, CRS Report for Congress, No. 32003, *Hatch-Waxman Related Provisions of the Medicare Prescription Drug Bills (H.R. 1 and S. 1): A Side-bySide Comparison* (Updated 2003). In a side-by-side comparison of H.R.1 and S.1 (the pending bills), the report states:

H.R. 1	S. 1
Allows the paragraph IV ANDA applicant to request a declaratory judgment regarding the validity of the patent if an infringement suit is not filed within 45 days of notification. However, if sued, the generic firm may file a counter claim to require the patent holder make changes to the Orange Book listings. No damages are to be awarded in either case.	If a patent owner does not file an infringement suit within 45 days of notification of a paragraph IV ANDA, the ANDA applicant may request a declaratory judgment regarding the validity of the patent. However, if sued, the generic firm may file a counter claim to require the patent holder make changes to the Orange Book listings. No damages are to be awarded in either case.

Id. at 5.

b.

In the floor debate in the Senate on November 24, 2003, this view of the scope of a counterclaim is discussed: 149 Cong. Rec. S 15746:

> The Gregg-Schumer amendments to the Hatch-Waxman Act would put an end to the practice of brand companies listing frivolous patents
>
> for the sole purpose of automatically delaying generic approval.
>
> * * *
>
> Third, the provisions enforce the patent listing requirements at the FDA by allowing a generic applicant, when it has been sued for patent infringement, to file a counterclaim to have the brand drug company delist the patent or correct the patent information in FDA's Orange Book.

149 Cong. Rec. 51546 (2003) (statement of Sen. Schumer).

c.

The broad scope of the counterclaim provision is discussed in a commentary on Greater Access to Affordable Pharmaceutical Act, S. 1225, 108th Cong. — a precursor to Pub. L. No. 108-173. Sec. 2(a)(C)(iii)(II) of the bill contained a provision reading:

> (II) COUNTERCLAIM TO INFRINGEMENT ACTION
>
> (aa) IN GENERAL — if the owner of the patent brings a patent infringement action against the applicant, the applicant may assert

a counterclaim seeking an order requiring the patent owner to correct or delete patent information filed by the patent owner under subsection (b) or (c) on the ground that the patent does not claim —

(AA) the drug for which the application was approved; or (BB) an approved method of using the drug.

(bb) NO DAMAGES — An applicant shall not be entitled to damages on a counterclaim under item (aa)

(cc) NO INDEPENDENT CAUSE OF ACTION — Item (aa) does not authorize the assertion of a claim described in item (aa) in any civil action or proceeding other than a counterclaim described in item (aa)

Sarah Eurek, in explaining the subsection, says:

Provisions Regarding Orange Book Listings:

Unlike the FDA regulations, the GAAP does not specify which patents may or may not be listed in the Orange Book. However, it does create a new mechanism for challenging improper Orange Book listings. If a name-brand company lists a questionable patent and sues a generic applicant for violating that patent in order to trigger the 30-month stay, the GAAP allows the generic company to file a counterclaim, arguing that the patent should not have been listed. Subsequently, an order may be entered requiring the patent owner to correct or delete the patent information in the Orange Book. This provides an official mechanism for unlisting improper patents from the Orange

> Book, one which previously did not exist under current law or FDA regulations.

Sarah E. Eurek, Note, *Hatch-Waxman Reform and Accelerated Market Entry of Generic Drugs: Is Faster Necessarily Better?*, 2003 Duke L. & Tech. Rev. 0018.

d.

Post-enactment of Pub. L. No. 108-173 the Congressional Research Service said:

> Under the original act, the role of the FDA in adjudicating Orange Book listing disagreements is limited. If a generic pharmaceutical company disputes the accuracy of an Orange Book listing, that enterprise must present the grounds for disagreement to the FDA in writing. The FDA will then request that the NDA holder confirm the propriety of the listing. Unless the NDA holder withdraws or amends the listing, the FDA will not alter the patent information in the Orange Book.

Congressional Research Service, CRS Report for Congress, No. RL 32377, *The Hatch- Waxman Act: Legislative Changes Affecting Pharmaceutical Patents* 5 (2004). It went on to say:

> If sued, the generic firm may file a counter claim to require the patent holder make changes in the Orange Book listings. The generic firm may request that certain patents be delisted because they do not claim the drug to which they are attached. No monetary damages are to be awarded.

Id. at 9.

IV.

A.

Novo's assertion that the counterclaim provisions of Pub. L. No. 108-173, § 355(j)(5)(C)(ii) are limited solely to a correction of the patent number and the expiration date of the patent linked to an incorrect Use Code narrative in the Orange Book are belied by what has been discussed above.

As quoted above, FDA's Form 3542 requires that a Use Code narrative accurately describe each approved method of use *claimed* by a patent listed in the Orange Book. The narrative is limited to those approved uses of the drug product that the patent claims. *See also* 68 Fed. Reg. 36,682 (attached Exhibit A) and 21 C.F.R. § 314.53(c)(2)(ii)(P). In expanding the required patent information beyond the patent number and expiration date, FDA cited as its authority section 701(a) of the act which provides, "The authority to promulgate regulations for the efficient enforcement of this Act, except as otherwise provided in this section, is hereby vested in the Secretary." 21 U.S.C. § 371(a).

The FDA's administration of the Orange Book is strictly ministerial. The FDA makes no judgment on whether or not a Use Code narrative comports to the use of the drug product covered by the patent. The FDA accepts what the application for approval of the drug product states the patent covers. *See aaiPharma Inc.* v. *Thompson*, 296 F.3d 227, 234 (4th Cir. 2002).

Mylan pointed up a flaw in Hatch-Waxman: the fact that an applicant for ANDA could be seriously disadvantaged by an incorrect Use Code narrative because of a lack of an opportunity to challenge it. Senator Schumer in his floor comments quoted above

described how the counterclaim provision would give a generic drug manufacturer processing an ANDA the opportunity to challenge a Use Code narrative improperly impeding the processing of the ANDA.

Novo's position that only the fact of the patent's listing in the Orange Book and its expiration date could be challenged by a generic drug manufacturer is undercut not only by the history of § 355(j)(5)(C)(ii), but also by the fact that nowhere in that history is there mention of just striking the patent or compelling a change in its expiration date discussed. What was discussed regarding the Use Code narrative was the difficulty a generic drug manufacturer faced in any effort to challenge an improper use code narrative. Hobbled by an improper use code narrative, the generic drug manufacturer was given its day in court. Only a court could offer it relief if its position was correct, and denial of Novo's motion does just that. Caraco is entitled to its day in court on its claim that the May 06, 2004, filing by Novo was improper and a misuse of its rights under Hatch-Waxman.

B.

As is the case of its reliance on *Mylan* to support its challenge to Caraco's Counterclaim, Novo again relies on that 2001 decision to supports its motion to strike Caraco's Sixth Affirmative Defense (patent misuse). Novo quotes pages 1331-32 of that decision to the effect that the Hatch-Waxman Act neither explicitly provides for, nor points to any intent to provide, such a defense based on improper Orange Book listing. *Mylan* was not an infringement action where the defense of patent misuse was raised, but rather a declaratory judgment in the form of an attempted

private cause of action against the FDA and the patent owner.

The Counterclaims sections of a conference report accompanying the Medicare, Prescription Drug, Improvement and Modernization Act of 2003 directly contradicts Novo's reliance on the earlier *Mylan* decision:

> Section 1101 of the Conference agreement prohibits the recovery of damages resulting from a successful counterclaim in a paragraph IV patent suit by an ANDA applicant seeking removal of a patent listed in the Orange Book. *It is not the intent of Congress to prohibit recovery by a counterclaimant in a paragraph IV suit of anti-trust or any other damages as a result of the improper listing of a patent in the Orange* Book. The language found in this section simply means that *in the absence of any other cause of action,* a ruling in favor of the counterclaimant resulting in the removal of the patent does not entitle the countercliamant to recover damages. (emphasis added)

H.R. Rep. No. 108-391, at 836 (2003).

In *Astra Aktiebolag* v. *Kremers Urban Development* Co., 61 U.S.P.Q.2d 1767 (S.D.N.Y. 2001), the court denied a motion to dismiss portions of the defendant's Answer and Counterclaim alleging misuse as to the asserted '499 patent. The allegation was that the patent owner falsely certified to the FCA that such patent covered the approved product and that such false certification forced defendant to file a Paragraph IV certificate. The court stated that "the elements of an allegation of patent misuse include a patentee's impermissible use of its patent to broaden

the physical or temporal scope of its patent with an anticompetitive *effect." Id.* at 1768. It held that "these allegations are sufficient to state a claim of patent misuse with respect to the '499 patent." *Id.*

The *Astra* decision, rather than the *Schwarz Pharma, Inc* v. *Teva Pharmaceuticals USA, Inc.*, 2005 WL 4158850 (D.N.J. Feb. 4, 2005) decision cited by Novo, is the better reasoned decision. *Schwarz* misconstrues *Mylan* and fails to distinguish the nature of the suit. Caraco's Sixth Affirmative Defense alleges sufficient facts and theory of defense to survive Novo's Motion to Strike under Rule 12(f).

s/Avern Cohn
AVERN COHN
UNITED STATES DISTRICT JUDGE

Dated: August 31, 2009

I hereby certify that a copy of the foregoing document was mailed to the attorneys of record on this date, August 31, 2009, by electronic and/or ordinary mail.

s/LaShawn R. Saulsberry
Case Manager, (313) 234-5160

05-40188 Novo Nordisk, et al v. Caraco Pharm, et al

EXHIBIT A

1.

21 U.S.C. § 355(b)(1)(G) reads in part:

> (G) The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. . .Upon approval of the application, the secretary shall publish information submitted under the two preceding sentences.

2.

21 C.F.R. § 314.53 Submission of Patent Information, reads in part:

> An applicant. . shall submit the required information on the declaration form. . .for each patent that claims. . .a method of using the drug. . .and with respect to which a claim of patent infringement could reasonably be asserted. . .For patents that claim a method of use, the applicant shall submit information only on those patents that claim indications or other conditions of use that are described in the pending or approved application. The applicant shall separately identify each pending or approved method of use and related patent claim. For approved applications, the applicant submitting the method-of-use patent shall

identify with specificity the section of the approved labeling that corresponds to the method of use claimed by the patent submitted.

3.

68 Fed. Reg. 36,682-83, 97-98 reads in part:

[W]e do require identification of individual claims for method-ofuse patents. The declarant must describe each individual method of use for which a patent is submitted for listing, and identify the corresponding language found in the labeling of the approved NDA that corresponds to that method of use. This information will expedite our review of ANDA and 505(b)(2) applications that do not seek approval for all the approved uses. In determining whether an ANDA applicant can "carve out" the method of use, rather than certify to the listed patent, we will rely on the description of the approved use provided by the NDA holder or patent owner in the patent declaration and listed in the Orange Book.

The need for accurate and detailed information related to the approved methods of use claimed in the patent being submitted for listing is underscored by the decision in *Purepac Pharm. Co.* v. *Thompson,* 238 F.Supp.2d 191 (D.D.C. 2002). In that case, the NDA holder submitted information on a patent claiming what was later determined to be an unapproved use of the approved drug product. This submission was accompanied by the required signed declaration from the NDA holder that the patent covered the method of use for the approved product. Accordingly, we listed the patent and

the use code information submitted with the patent. Years later, well after litigation over this patent was underway, the NDA holder clarified to FDA that the patent did not, in fact, claim the use for which the NDA was approved.

This submission of inappropriate patent information led to confusion and then to litigation over an ANDA applicant's obligation to submit either a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the act or a "section viii" statement under section 505(j)(2)(A)(viii) of the act. The section viii statement, which is also applicable to 505(b)(2) applications, permits the ANDA or 505(b)(2) applicant to avoid certifying to a patent by stating that it is not seeking approval for the use claimed in the listed patent.

* * *

In the absence of explicit statutory language, we believe an approach that requires the NDA applicant or holder or patent owner to identify the approved methods of use protected by the patent is most consistent with the general balance adopted in Hatch-Waxman.

* * *

To effectively implement the certification and section viii statement provisions set out in the statute, we must have adequate information concerning method-of-use patents.

Since 1994, we have requested, but not required, that NDA applicants submit to FDA information on the approved use claimed by the

patent. Since the *Purepac* case and other instances have raised questions about what aspects of the approved drug are claimed by a listed use patent, we believe that it is necessary that an NDA holder submit more specific information on the approved methods of use protected by a submitted patent. Only with this information can we determine what submission is required of the ANDA and 505(b)(2) applicants referencing the approved drug.

* * *

After considering the comments, and in light of the previously described litigation, we have determined that it is more efficient and accurate to ask the NDA holder to give us the exact use code description to be published in the Orange Book. Use codes are intended to alert ANDA and 505(b)(2) applicants to the existence of a patent that claims an approved use. They are not meant to substitute for the applicant's review of the patent and the approved labeling. . . .The declaration, which includes the complete description of the method-of-use claim and the corresponding language in the labeling of the approved drug, will be publicly available after NDA approval.

(Comment 8) Several comments stated that parties, such as generic drug companies and even third parties, need a method for challenging patent listings or for de-listing patents in the Orange Book. Some comments explained that the lack of an administrative procedure for challenging patent listings either encouraged NDA applicants to submit inappropriate

patent information, or did not deter the practice, to delay generic competition. A number of comments maintained that FDA has more than a ministerial role and should review patents to determine if they meet the requirements for listing.

* * *

In addition to the absence of any statutory basis for a substantive agency review of patents, we have long observed that we lack expertise in patent matters. An administrative process for reviewing patents, assessing patent challenges, and de-listing patents would involve patent law issues that are outside both our expertise and our authority. Although we will continue to relay questions about the accuracy of a patent submission to the NDA holder (see §314.53(f)), our patent listing role remains ministerial.

* * *

V. Legal Authority

Our principal legal authority for the final rule is section 505 of the act, in conjunction with our general rulemaking authority in section 701(a) (21 USC 371) of the act. Section 505(b) and (c) of the act describes the contents of an NDA and 505(b)(2) application, including the patent submission and patent certification requirements.

bioavailability studies). Such investigations must have been conducted or sponsored by the applicant and must have been essential to approval of the application. If these requirements are met, the approval of a subsequent ANDA or an application described in Section 505(b)(2) of the Act may not be *made effective* for the same drug or use, if for a new indication, before the expiration of *three years* from the date of approval of the original application. If an applicant has exclusivity for a new application or 505(b)(2) application for the drug product with indications or use, this does not preclude the approval of an ANDA or 505(b)(2) application not covered by the exclusivity.

(3) A supplement to a new drug application for a drug containing a previously approved active ingredient including (any ester or salt of the active ingredient) approved after September 24, 1984, that contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the applicant. The approval of a subsequent ANDA or 505(b)(2) application for a change approved in the supplement may not be *made effective* for *three years* from the date of approval of the original supplement.

The Act requires that patent information be filed with all newly submitted Section 505(b) drug applications. No NDA may be approved after September 24, 1984, without the submission of patent information to the Agency. Effective August 18, 2003, this information must be filed using FDA Form 3524a "Patent In-

formation Submitted with the Filing of an NDA, Amendment or Supplement".

Effective August 18, 2003, upon approval of an application, patent information for purposes of listing in the Orange Book must be submitted to the agency within 30 days of approval on FDA Form 3542 "Patent Information Submitted Upon and After Approval of an NDA or Supplement". Patent information on unapproved applications or on patents beyond the scope of the Act (i.e., process or manufacturing patents) will not be published. FDA form 3542 will be the only form used for the purposes of this publication.

The patents that FDA regards as covered by the statutory provisions for submission of patent information are: patents that claim the active ingredient(s); drug product patents which include formulation/composition patents; use patents for a particular approved indication or method of using the product; and certain other patents as detailed on FDA Form 3542. This information, as provided by the sponsor on FDA form 3542, will be published as described above.

A requirement for submission of patent information to FDA for certain old antibiotics became effective October 7, 2008 under section 4(b)(1) of the Q1 Act. A guidance for industry on this subject is available. Upon approval, patent numbers and expiration dates, in addition to certain other information on appropriate patents claiming drug products that are the subject of approved applications, will be published on a daily basis in the Electronic Orange Book,

http://www.fda.gov/drugs/developmentapprovalprocess/ucm079068.htm

APPENDIX F

UNITED STATES CODE

Title 21--Food and Drugs (Refs & Annos)

Chapter 9--Federal Food, Drug, and Cosmetic Act

Subchapter V--Drugs and Devices

Part A--Drugs and Devices

§ 355. New drugs

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug, and (G) any assessments required under section 355c of this title. The applicant shall file with the application the patent number and the expiration date

of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A).

(2) An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include--

(A) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is re-

quired to be filed under paragraph (1) or subsection (c) of this section--

(i) that such patent information has not been filed,

(ii) that such patent has expired,

(iii) of the date on which such patent will expire, or

(iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(B) if with respect to the drug for which investigations described in paragraph (1)(A) were conducted information was filed under paragraph (1) or subsection (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

(3) Notice of opinion that patent is invalid or will not be infringed

(A) Agreement to give notice

An applicant that makes a certification described in paragraph (2)(A)(iv) shall include in the application a statement that the applicant will give notice as required by this paragraph.

(B) Timing of notice

An applicant that makes a certification described in paragraph (2)(A)(iv) shall give notice as required under this paragraph--

(i) if the certification is in the application, not later than 20 days after the date of the postmark on the notice with which the Secretary informs the applicant that the application has been filed; or

(ii) if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.

(C) Recipients of notice

An applicant required under this paragraph to give notice shall give notice to--

(i) each owner of the patent that is the subject of the certification (or a representative of the owner designated to receive such a notice); and

(ii) the holder of the approved application under this subsection for the drug that is claimed by the patent or a use of which is claimed by the patent (or a representative of the holder designated to receive such a notice).

(D) Contents of notice

A notice required under this paragraph shall--

(i) state that an application that contains data from bioavailability or bioequivalence studies has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification; and

(ii) include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.

(4)(A) An applicant may not amend or supplement an application referred to in paragraph (2) to seek ap-

proval of a drug that is a different drug than the drug identified in the application as submitted to the Secretary.

(B) With respect to the drug for which such an application is submitted, nothing in this subsection or subsection (c)(3) of this section prohibits an applicant from amending or supplementing the application to seek approval of a different strength.

(5)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1) or under section 262 of Title 42, which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection or section 262 of Title 42 if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim or, with respect to an applicant for approval of a biological product under section 262(k) of Title 42, any necessary clinical study or studies. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of the clinical trials. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant upon request.

(C) Any agreement regarding the parameters of the design and size of clinical trials of a new drug under this paragraph that is reached between the Secretary

and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except--

(i) with the written agreement of the sponsor or applicant; or

(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance division personnel unless such field or compliance division personnel demonstrate to the reviewing division why such decision should be modified.

(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection or section 262 of Title 42 (including all scientific

and medical matters, chemistry, manufacturing, and controls).

(6) An application submitted under this subsection shall be accompanied by the certification required under section 282(j)(5)(B) of Title 42. Such certification shall not be considered an element of such application.

(c) Period for approval of application; period for, notice, and expedition of hearing; period for issuance of order

(1) Within one hundred and eighty days after the filing of an application under subsection (b) of this section, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either--

(A) Approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) of this section applies, or

(B) Give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) of this section on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(2) If the patent information described in subsection (b) of this section could not be filed with the submis-

sion of an application under subsection (b) of this section because the application was filed before the patent information was required under subsection (b) of this section or a patent was issued after the application was approved under such subsection, the holder of an approved application shall file with the Secretary the patent number and the expiration date of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If the holder of an approved application could not file patent information under subsection (b) of this section because it was not required at the time the application was approved, the holder shall file such information under this subsection not later than thirty days after September 24, 1984, and if the holder of an approved application could not file patent information under subsection (b) of this section because no patent had been issued when an application was filed or approved, the holder shall file such information under this subsection not later than thirty days after the date the patent involved is issued. Upon the submission of patent information under this subsection, the Secretary shall publish it.

(3) The approval of an application filed under subsection (b) of this section which contains a certification required by paragraph (2) of such subsection shall be made effective on the last applicable date determined by applying the following to each certification made under subsection (b)(2)(A) of this section:

(A) If the applicant only made a certification described in clause (i) or (ii) of subsection (b)(2)(A) of

this section or in both such clauses, the approval may be made effective immediately.

(B) If the applicant made a certification described in clause (iii) of subsection (b)(2)(A) of this section, the approval may be made effective on the date certified under clause (iii).

(C) If the applicant made a certification described in clause (iv) of subsection (b)(2)(A) of this section, the approval shall be made effective immediately unless, before the expiration of 45 days after the date on which the notice described in subsection (b)(3) of this section is received, an action is brought for infringement of the patent that is the subject of the certification and for which information was submitted to the Secretary under paragraph (2) or subsection (b)(1) of this section before the date on which the application (excluding an amendment or supplement to the application) was submitted. If such an action is brought before the expiration of such days, the approval may be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under subsection (b)(3) of this section or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that--

(i) if before the expiration of such period the district court decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the approval shall be made effective on--

(I) the date on which the court enters judgment reflecting the decision; or

(II) the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed;

(ii) if before the expiration of such period the district court decides that the patent has been infringed--

(I) if the judgment of the district court is appealed, the approval shall be made effective on--

(aa) the date on which the court of appeals decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity); or

(bb) the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid or not infringed; or

(II) if the judgment of the district court is not appealed or is affirmed, the approval shall be made effective on the date specified by the district court in a court order under section 271(e)(4)(A) of Title 35;

(iii) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective as provided in clause (i); or

(iv) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court de-

cides that such patent has been infringed, the approval shall be made effective as provided in clause (ii).

In such an action, each of the parties shall reasonably cooperate in expediting the action.

(D) Civil action to obtain patent certainty

(i) Declaratory judgment absent infringement action

(I) In general

No action may be brought under section 2201 of Title 28, by an applicant referred to in subsection (b)(2) of this section for a declaratory judgment with respect to a patent which is the subject of the certification referred to in subparagraph (C) unless--

(aa) the 45-day period referred to in such subparagraph has expired;

(bb) neither the owner of such patent nor the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brought a civil action against the applicant for infringement of the patent before the expiration of such period; and

(cc) in any case in which the notice provided under paragraph (2)(B) relates to noninfringement, the notice was accompanied by a document described in subclause (III).

(II) Filing of civil action

If the conditions described in items (aa), (bb), and as applicable, (cc) of subclause (I) have been met, the applicant referred to in such subclause may, in accordance with section 2201 of Title 28, bring a civil action under such section against the owner or holder referred to in such subclause (but not against any

owner or holder that has brought such a civil action against the applicant, unless that civil action was dismissed without prejudice) for a declaratory judgment that the patent is invalid or will not be infringed by the drug for which the applicant seeks approval, except that such civil action may be brought for a declaratory judgment that the patent will not be infringed only in a case in which the condition described in subclause (I)(cc) is applicable. A civil action referred to in this subclause shall be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

(III) Offer of confidential access to application

For purposes of subclause (I)(cc), the document described in this subclause is a document providing an offer of confidential access to the application that is in the custody of the applicant referred to in subsection (b)(2) of this section for the purpose of determining whether an action referred to in subparagraph (C) should be brought. The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an

offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under subsection (b)(2)(A)(iv) of this section and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement.

(ii) Counterclaim to infringement action

(I) In general

If an owner of the patent or the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) of this section or this subsection on the ground that the patent does not claim either--

(aa) the drug for which the application was approved; or

(bb) an approved method of using the drug.

(II) No independent cause of action

Subclause (I) does not authorize the assertion of a claim described in subclause (I) in any civil action or proceeding other than a counterclaim described in subclause (I).

(iii) No damages

An applicant shall not be entitled to damages in a civil action under clause (i) or a counterclaim under clause (ii).

(E)(i) If an application (other than an abbreviated new drug application) submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of another application for a drug for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted effective before the expiration of ten years from the date of the approval of the application previously approved under subsection (b) of this section.

(ii) If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application which refers to the drug for which the subsection (b) application was submitted and for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations

were conducted may be submitted under subsection (b) of this section before the expiration of five years from the date of the approval of the application under subsection (b) of this section, except that such an application may be submitted under subsection (b) of this section after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in clause (iv) of subsection (b)(2)(A) of this section. The approval of such an application shall be made effective in accordance with this paragraph except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (C) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) of this section for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application

under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

(iv) If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailabilty [FN1] studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under subsection (b) of this section for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

(v) If an application (or supplement to an application) submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsec-

tion and for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted and which refers to the drug for which the subsection (b) application was submitted effective before the expiration of two years from September 24, 1984.

(4) A drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the drug and to obtain approval for the drug prior to manufacture of the drug in a larger facility, unless the Secretary makes a determination that a full scale production facility is necessary to ensure the safety or effectiveness of the drug.

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and

packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the patent information prescribed by subsection (b) of this section; or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (ob-

tained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence.

(e) Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) the patent information prescribed by subsection (c) of this section was not filed within thirty days after the receipt of written notice from the Secretary specifying

the failure to file such information; or (5) that the application contains any untrue statement of a material fact: Provided, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application submitted under subsection (b) or (j) of this section with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (k) of this section or to comply with the notice requirements of section 360(k)(2) of this title, or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was ap-

proved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based. The Secretary may withdraw the approval of an application submitted under this section, or suspend the approval of such an application, as provided under this subsection, without first ordering the applicant to submit an assessment of the approved risk evaluation and mitigation strategy for the drug under section 355-1(g)(2)(D) of this title.

(f) Revocation of order refusing, withdrawing or suspending approval of application

Whenever the Secretary finds that the facts so require, he shall revoke any previous order under subsection (d) or (e) of this section refusing, withdrawing, or suspending approval of an application and shall approve such application or reinstate such approval, as may be appropriate.

(g) Service of orders

Orders of the Secretary issued under this section shall be served (1) in person by any officer or employee of the Department designated by the Secretary or (2) by mailing the order by registered mail or by certified mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) Appeal from order

An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such ap-

peal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of Title 28. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recom-

mendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of Title 28. The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

(i) Exemptions of drugs for research; discretionary and mandatory conditions; direct reports to Secretary

(1) The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon--

(A) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing;

(B) the manufacturer or the sponsor of the investigation of a new drug proposed to be distributed to investigators for clinical testing obtaining a signed agreement from each of such investigators that patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to him, and that he will not sup-

ply such drug to any other investigator, or to clinics, for administration to human beings;

(C) the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b) of this section; and

(D) the submission to the Secretary by the manufacturer or the sponsor of the investigation of a new drug of a statement of intent regarding whether the manufacturer or sponsor has plans for assessing pediatric safety and efficacy.

(2) Subject to paragraph (3), a clinical investigation of a new drug may begin 30 days after the Secretary has received from the manufacturer or sponsor of the investigation a submission containing such information about the drug and the clinical investigation, including--

(A) information on design of the investigation and adequate reports of basic information, certified by the applicant to be accurate reports, necessary to assess the safety of the drug for use in clinical investigation; and

(B) adequate information on the chemistry and manufacturing of the drug, controls available for the drug, and primary data tabulations from animal or human studies.

(3)(A) At any time, the Secretary may prohibit the sponsor of an investigation from conducting the investigation (referred to in this paragraph as a "clinical hold") if the Secretary makes a determination described in subparagraph (B). The Secretary shall specify the basis for the clinical hold, including the specific information available to the Secretary which served as the basis for such clinical hold, and confirm such determination in writing.

(B) For purposes of subparagraph (A), a determination described in this subparagraph with respect to a clinical hold is that--

(i) the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation, taking into account the qualifications of the clinical investigators, information about the drug, the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved; or

(ii) the clinical hold should be issued for such other reasons as the Secretary may by regulation establish (including reasons established by regulation before November 21, 1997).

(C) Any written request to the Secretary from the sponsor of an investigation that a clinical hold be removed shall receive a decision, in writing and specifying the reasons therefor, within 30 days after receipt of such request. Any such request shall include sufficient information to support the removal of such clinical hold.

(4) Regulations under paragraph (1) shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, re-

quiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where it is not feasible or it is contrary to the best interests of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs. The Secretary shall update such regulations to require inclusion in the informed consent documents and process a statement that clinical trial information for such clinical investigation has been or will be submitted for inclusion in the registry data bank pursuant to subsection (j) of section 282 of Title 42.

(j) Abbreviated new drug applications

(1) Any person may file with the Secretary an abbreviated application for the approval of a new drug.

(2)(A) An abbreviated application for a new drug shall contain--

(i) information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed under paragraph (7) (hereinafter in this subsection referred to as a "listed drug");

(ii)(I) if the listed drug referred to in clause (i) has only one active ingredient, information to show that the active ingredient of the new drug is the same as that of the listed drug;

(II) if the listed drug referred to in clause (i) has more than one active ingredient, information to show that the active ingredients of the new drug are the same as those of the listed drug, or

(III) if the listed drug referred to in clause (i) has more than one active ingredient and if one of the active ingredients of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the other active ingredients of the new drug are the same as the active ingredients of the listed drug, information to show that the different active ingredient is an active ingredient of a listed drug or of a drug which does not meet the requirements of section 321(p) of this title, and such other information respecting the different active ingredient with respect to which the petition was filed as the Secretary may require;

(iii) information to show that the route of administration, the dosage form, and the strength of the new drug are the same as those of the listed drug referred to in clause (i) or, if the route of administration, the dosage form, or the strength of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), such information respecting the route of administration, dosage form, or strength with respect to which the petition was filed as the Secretary may require;

(iv) information to show that the new drug is bioequivalent to the listed drug referred to in clause (i), except that if the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the active ingredients of the new drug are of the same pharmacological or thera-

peutic class as those of the listed drug referred to in clause (i) and the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in clause (i);

(v) information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers;

(vi) the items specified in clauses (B) through (F) of subsection (b)(1) of this section;

(vii) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the listed drug referred to in clause (i) or which claims a use for such listed drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (c) of this section--

(I) that such patent information has not been filed,

(II) that such patent has expired,

(III) of the date on which such patent will expire, or

(IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(viii) if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) of this section for a method of use patent which does not claim a use for which the applicant is seek-

ing approval under this subsection, a statement that the method of use patent does not claim such a use.

The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).

(B) Notice of opinion that patent is invalid or will not be infringed

(i) Agreement to give notice

An applicant that makes a certification described in subparagraph (A)(vii)(IV) shall include in the application a statement that the applicant will give notice as required by this subparagraph.

(ii) Timing of notice

An applicant that makes a certification described in subparagraph (A)(vii)(IV) shall give notice as required under this subparagraph--

(I) if the certification is in the application, not later than 20 days after the date of the postmark on the notice with which the Secretary informs the applicant that the application has been filed; or

(II) if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.

(iii) Recipients of notice

An applicant required under this subparagraph to give notice shall give notice to--

(I) each owner of the patent that is the subject of the certification (or a representative of the owner designated to receive such a notice); and

(II) the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent (or a representative of the holder designated to receive such a notice).

(iv) Contents of notice

A notice required under this subparagraph shall--

(I) state that an application that contains data from bioavailability or bioequivalence studies has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification; and

(II) include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.

(C) If a person wants to submit an abbreviated application for a new drug which has a different active ingredient or whose route of administration, dosage form, or strength differ from that of a listed drug, such person shall submit a petition to the Secretary seeking permission to file such an application. The Secretary shall approve or disapprove a petition submitted under this subparagraph within ninety days of the date the petition is submitted. The Secretary shall approve such a petition unless the Secretary finds--

(i) that investigations must be conducted to show the safety and effectiveness of the drug or of any of its ac-

tive ingredients, the route of administration, the dosage form, or strength which differ from the listed drug; or

(ii) that any drug with a different active ingredient may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted in an abbreviated application.

(D)(i) An applicant may not amend or supplement an application to seek approval of a drug referring to a different listed drug from the listed drug identified in the application as submitted to the Secretary.

(ii) With respect to the drug for which an application is submitted, nothing in this subsection prohibits an applicant from amending or supplementing the application to seek approval of a different strength.

(iii) Within 60 days after December 8, 2003, the Secretary shall issue guidance defining the term "listed drug" for purposes of this subparagraph.

(3)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1), which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of bioavailability and bioequivalence studies needed for approval of such application. The sponsor

or applicant shall provide information necessary for discussion and agreement on the design and size of such studies. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant.

(C) Any agreement regarding the parameters of design and size of bioavailability and bioequivalence studies of a drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except--

(i) with the written agreement of the sponsor or applicant; or

(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance office personnel unless such field or compliance office personnel demonstrate to the reviewing division why such decision should be modified.

(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection (including scientific matters, chemistry, manufacturing, and controls).

(4) Subject to paragraph (5), the Secretary shall approve an application for a drug unless the Secretary finds--

(A) the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity;

(B) information submitted with the application is insufficient to show that each of the proposed conditions of use have been previously approved for the listed drug referred to in the application;

(C)(i) if the listed drug has only one active ingredient, information submitted with the application is insufficient to show that the active ingredient is the same as that of the listed drug;

(ii) if the listed drug has more than one active ingredient, information submitted with the application is insufficient to show that the active ingredients are the same as the active ingredients of the listed drug, or

(iii) if the listed drug has more than one active ingredient and if the application is for a drug which has an active ingredient different from the listed drug, in-

formation submitted with the application is insufficient to show--

(I) that the other active ingredients are the same as the active ingredients of the listed drug, or

(II) that the different active ingredient is an active ingredient of a listed drug or a drug which does not meet the requirements of section 321(p) of this title,

or no petition to file an application for the drug with the different ingredient was approved under paragraph (2)(C);

(D)(i) if the application is for a drug whose route of administration, dosage form, or strength of the drug is the same as the route of administration, dosage form, or strength of the listed drug referred to in the application, information submitted in the application is insufficient to show that the route of administration, dosage form, or strength is the same as that of the listed drug, or

(ii) if the application is for a drug whose route of administration, dosage form, or strength of the drug is different from that of the listed drug referred to in the application, no petition to file an application for the drug with the different route of administration, dosage form, or strength was approved under paragraph (2)(C);

(E) if the application was filed pursuant to the approval of a petition under paragraph (2)(C), the application did not contain the information required by the Secretary respecting the active ingredient, route of administration, dosage form, or strength which is not the same;

(F) information submitted in the application is insufficient to show that the drug is bioequivalent to the

listed drug referred to in the application or, if the application was filed pursuant to a petition approved under paragraph (2)(C), information submitted in the application is insufficient to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in paragraph (2)(A)(i) and that the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in such paragraph;

(G) information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the application except for changes required because of differences approved under a petition filed under paragraph (2)(C) or because the drug and the listed drug are produced or distributed by different manufacturers;

(H) information submitted in the application or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included;

(I) the approval under subsection (c) of this section of the listed drug referred to in the application under this subsection has been withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section, the Secretary has published a notice of opportunity for hearing to withdraw approval

of the listed drug under subsection (c) of this section for grounds described in the first sentence of subsection (e) of this section, the approval under this subsection of the listed drug referred to in the application under this subsection has been withdrawn or suspended under paragraph (6), or the Secretary has determined that the listed drug has been withdrawn from sale for safety or effectiveness reasons;

(J) the application does not meet any other requirement of paragraph (2)(A); or

(K) the application contains an untrue statement of material fact.

(5)(A) Within one hundred and eighty days of the initial receipt of an application under paragraph (2) or within such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall approve or disapprove the application.

(B) The approval of an application submitted under paragraph (2) shall be made effective on the last applicable date determined by applying the following to each certification made under paragraph (2)(A)(vii):

(i) If the applicant only made a certification described in subclause (I) or (II) of paragraph (2)(A)(vii) or in both such subclauses, the approval may be made effective immediately.

(ii) If the applicant made a certification described in subclause (III) of paragraph (2)(A)(vii), the approval may be made effective on the date certified under subclause (III).

(iii) If the applicant made a certification described in subclause (IV) of paragraph (2)(A)(vii), the approval shall be made effective immediately unless, before the expiration of 45 days after the date on which the

notice described in paragraph (2)(B) is received, an action is brought for infringement of the patent that is the subject of the certification and for which information was submitted to the Secretary under subsection (b)(1) or (c)(2) of this section before the date on which the application (excluding an amendment or supplement to the application), which the Secretary later determines to be substantially complete, was submitted. If such an action is brought before the expiration of such days, the approval shall be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under paragraph (2)(B)(i) or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that--

(I) if before the expiration of such period the district court decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the approval shall be made effective on--

(aa) the date on which the court enters judgment reflecting the decision; or

(bb) the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed;

(II) if before the expiration of such period the district court decides that the patent has been infringed--

(aa) if the judgment of the district court is appealed, the approval shall be made effective on--

(AA) the date on which the court of appeals decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity); or

(BB) the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid or not infringed; or

(bb) if the judgment of the district court is not appealed or is affirmed, the approval shall be made effective on the date specified by the district court in a court order under section 271(e)(4)(A) of Title 35;

(III) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective as provided in subclause (I); or

(IV) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent has been infringed, the approval shall be made effective as provided in subclause (II).

In such an action, each of the parties shall reasonably cooperate in expediting the action.

(iv) 180-day exclusivity period

(I) Effectiveness of application

Subject to subparagraph (D), if the application contains a certification described in paragraph (2)(A)(vii)(IV) and is for a drug for which a first applicant has submitted an application containing such a certification, the application shall be made effective on the date that is 180 days after the date of the first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant.

(II) Definitions

In this paragraph:

(aa) 180-day exclusivity period

The term "180-day exclusivity period" means the 180-day period ending on the day before the date on which an application submitted by an applicant other than a first applicant could become effective under this clause.

(bb) First applicant

As used in this subsection, the term "first applicant" means an applicant that, on the first day on which a substantially complete application containing a certification described in paragraph (2)(A)(vii)(IV) is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a certification described in paragraph (2)(A)(vii)(IV) for the drug.

(cc) Substantially complete application

As used in this subsection, the term "substantially complete application" means an application under this subsection that on its face is sufficiently complete to permit a substantive review and contains all the information required by paragraph (2)(A).

(dd) Tentative approval

(AA) In general

The term "tentative approval" means notification to an applicant by the Secretary that an application under this subsection meets the requirements of paragraph (2)(A), but cannot receive effective approval because the application does not meet the requirements of this subparagraph, there is a period of exclusivity for the listed drug under subparagraph (F) or section 355a of this title, or there is a 7-year period of exclusivity for the listed drug under section 360cc of this title.

(BB) Limitation

A drug that is granted tentative approval by the Secretary is not an approved drug and shall not have an effective approval until the Secretary issues an approval after any necessary additional review of the application.

(C) Civil action to obtain patent certainty

(i) Declaratory judgment absent infringement action

(I) In general

No action may be brought under section 2201 of Title 28, by an applicant under paragraph (2) for a declaratory judgment with respect to a patent which is the subject of the certification referred to in subparagraph (B)(iii) unless--

(aa) the 45-day period referred to in such subparagraph has expired;

(bb) neither the owner of such patent nor the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brought a

civil action against the applicant for infringement of the patent before the expiration of such period; and

(cc) in any case in which the notice provided under paragraph (2)(B) relates to noninfringement, the notice was accompanied by a document described in subclause (III).

(II) Filing of civil action

If the conditions described in items (aa), (bb), and as applicable, (cc) of subclause (I) have been met, the applicant referred to in such subclause may, in accordance with section 2201 of Title 28, bring a civil action under such section against the owner or holder referred to in such subclause (but not against any owner or holder that has brought such a civil action against the applicant, unless that civil action was dismissed without prejudice) for a declaratory judgment that the patent is invalid or will not be infringed by the drug for which the applicant seeks approval, except that such civil action may be brought for a declaratory judgment that the patent will not be infringed only in a case in which the condition described in subclause (I)(cc) is applicable. A civil action referred to in this subclause shall be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

(III) Offer of confidential access to application

For purposes of subclause (I)(cc), the document described in this subclause is a document providing an offer of confidential access to the application that is in the custody of the applicant under paragraph (2) for the purpose of determining whether an action referred to in subparagraph (B)(iii) should be brought. The document providing the offer of confidential ac-

cess shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV) and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement.

(ii) Counterclaim to infringement action

(I) In general

If an owner of the patent or the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection

(b) or (c) of this section on the ground that the patent does not claim either--

(aa) the drug for which the application was approved; or

(bb) an approved method of using the drug.

(II) No independent cause of action

Subclause (I) does not authorize the assertion of a claim described in subclause (I) in any civil action or proceeding other than a counterclaim described in subclause (I).

(iii) No damages

An applicant shall not be entitled to damages in a civil action under clause (i) or a counterclaim under clause (ii).

(D) Forfeiture of 180-day exclusivity period

(i) Definition of forfeiture event

In this subparagraph, the term "forfeiture event", with respect to an application under this subsection, means the occurrence of any of the following:

(I) Failure to market

The first applicant fails to market the drug by the later of--

(aa) the earlier of the date that is--

(AA) 75 days after the date on which the approval of the application of the first applicant is made effective under subparagraph (B)(iii); or

(BB) 30 months after the date of submission of the application of the first applicant; or

(bb) with respect to the first applicant or any other applicant (which other applicant has received tentative approval), the date that is 75 days after the date as of which, as to each of the patents with respect to which the first applicant submitted and lawfully maintained a certification qualifying the first applicant for the 180-day exclusivity period under subparagraph (B)(iv), at least 1 of the following has occurred:

(AA) In an infringement action brought against that applicant with respect to the patent or in a declaratory judgment action brought by that applicant with respect to the patent, a court enters a final decision from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the patent is invalid or not infringed.

(BB) In an infringement action or a declaratory judgment action described in subitem (AA), a court signs a settlement order or consent decree that enters a final judgment that includes a finding that the patent is invalid or not infringed.

(CC) The patent information submitted under subsection (b) or (c) of this section is withdrawn by the holder of the application approved under subsection (b) of this section.

(II) Withdrawal of application

The first applicant withdraws the application or the Secretary considers the application to have been withdrawn as a result of a determination by the Secretary that the application does not meet the requirements for approval under paragraph (4).

(III) Amendment of certification

The first applicant amends or withdraws the certification for all of the patents with respect to which that applicant submitted a certification qualifying the applicant for the 180-day exclusivity period.

(IV) Failure to obtain tentative approval

The first applicant fails to obtain tentative approval of the application within 30 months after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed.

(V) Agreement with another applicant, the listed drug application holder, or a patent owner

The first applicant enters into an agreement with another applicant under this subsection for the drug, the holder of the application for the listed drug, or an owner of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV), the Federal Trade Commission or the Attorney General files a complaint, and there is a final decision of the Federal Trade Commission or the court with regard to the complaint from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the agreement has violated the antitrust laws (as defined in section 12 of Title 15, except that the term includes section 45 of Title 15 to the extent that that section applies to unfair methods of competition).

(VI) Expiration of all patents

All of the patents as to which the applicant submitted a certification qualifying it for the 180-day exclusivity period have expired.

(ii) Forfeiture

The 180-day exclusivity period described in subparagraph (B)(iv) shall be forfeited by a first applicant if a forfeiture event occurs with respect to that first applicant.

(iii) Subsequent applicant

If all first applicants forfeit the 180-day exclusivity period under clause (ii)--

(I) approval of any application containing a certification described in paragraph (2)(A)(vii)(IV) shall be made effective in accordance with subparagraph (B)(iii); and

(II) no applicant shall be eligible for a 180-day exclusivity period.

(E) If the Secretary decides to disapprove an application, the Secretary shall give the applicant notice of an opportunity for a hearing before the Secretary on the question of whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(F)(i) If an application (other than an abbreviated new drug application) submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on

September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted effective before the expiration of ten years from the date of the approval of the application under subsection (b) of this section.

(ii) If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b) of this section, except that such an application may be submitted under this subsection after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in subclause (IV) of paragraph (2)(A)(vii). The approval of such an application shall be made effective in accordance with subparagraph (B) except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (B)(iii) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active in-

gredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section for such drug.

(iv) If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section.

(v) If an application (or supplement to an application) submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection

(b) application was submitted or which refers to a change approved in a supplement to the subsection (b) application effective before the expiration of two years from September 24, 1984.

(6) If a drug approved under this subsection refers in its approved application to a drug the approval of which was withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section or was withdrawn or suspended under this paragraph or which, as determined by the Secretary, has been withdrawn from sale for safety or effectiveness reasons, the approval of the drug under this subsection shall be withdrawn or suspended--

(A) for the same period as the withdrawal or suspension under subsection (e) of this section or this paragraph, or

(B) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

(7)(A)(i) Within sixty days of September 24, 1984, the Secretary shall publish and make available to the public--

(I) a list in alphabetical order of the official and proprietary name of each drug which has been approved for safety and effectiveness under subsection (c) of this section before September 24, 1984;

(II) the date of approval if the drug is approved after 1981 and the number of the application which was approved; and

(III) whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications

filed under this subsection which will refer to the drug published.

(ii) Every thirty days after the publication of the first list under clause (i) the Secretary shall revise the list to include each drug which has been approved for safety and effectiveness under subsection (c) of this section or approved under this subsection during the thirty-day period.

(iii) When patent information submitted under subsection (b) or (c) of this section respecting a drug included on the list is to be published by the Secretary, the Secretary shall, in revisions made under clause (ii), include such information for such drug.

(B) A drug approved for safety and effectiveness under subsection (c) of this section or approved under this subsection shall, for purposes of this subsection, be considered to have been published under subparagraph (A) on the date of its approval or September 24, 1984, whichever is later.

(C) If the approval of a drug was withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section or was withdrawn or suspended under paragraph (6) or if the Secretary determines that a drug has been withdrawn from sale for safety or effectiveness reasons, it may not be published in the list under subparagraph (A) or, if the withdrawal or suspension occurred after its publication in such list, it shall be immediately removed from such list--

(i) for the same period as the withdrawal or suspension under subsection (e) of this section or paragraph (6), or

(ii) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

A notice of the removal shall be published in the Federal Register.

(8) For purposes of this subsection:

(A)(i) The term "bioavailability" means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.

(ii) For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action.

(B) A drug shall be considered to be bioequivalent to a listed drug if--

(i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or

(ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is

reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

(C) For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

(9) The Secretary shall, with respect to each application submitted under this subsection, maintain a record of--

(A) the name of the applicant,

(B) the name of the drug covered by the application,

(C) the name of each person to whom the review of the chemistry of the application was assigned and the date of such assignment, and

(D) the name of each person to whom the bioequivalence review for such application was assigned and the date of such assignment.

The information the Secretary is required to maintain under this paragraph with respect to an application submitted under this subsection shall be made available to the public after the approval of such application.

(10)(A) If the proposed labeling of a drug that is the subject of an application under this subsection differs from the listed drug due to a labeling revision described under clause (i), the drug that is the subject of such application shall, notwithstanding any other provision of this chapter, be eligible for approval and

shall not be considered misbranded under section 352 of this title if--

(i) the application is otherwise eligible for approval under this subsection but for expiration of patent, an exclusivity period, or of a delay in approval described in paragraph (5)(B)(iii), and a revision to the labeling of the listed drug has been approved by the Secretary within 60 days of such expiration;

(ii) the labeling revision described under clause (i) does not include a change to the "Warnings" section of the labeling;

(iii) the sponsor of the application under this subsection agrees to submit revised labeling of the drug that is the subject of such application not later than 60 days after the notification of any changes to such labeling required by the Secretary; and

(iv) such application otherwise meets the applicable requirements for approval under this subsection.

(B) If, after a labeling revision described in subparagraph (A)(i), the Secretary determines that the continued presence in interstate commerce of the labeling of the listed drug (as in effect before the revision described in subparagraph (A)(i)) adversely impacts the safe use of the drug, no application under this subsection shall be eligible for approval with such labeling.

(k) Records and reports; required information; regulations and orders; access to records

(1) In the case of any drug for which an approval of an application filed under subsection (b) or (j) of this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and

other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section. Regulations and orders issued under this subsection and under subsection (i) of this section shall have due regard for the professional ethics of the medical profession and the interests of patients and shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulations or orders are applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this section to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

(3) Active postmarket risk identification

(A) Definition

In this paragraph, the term "data" refers to information with respect to a drug approved under this section or under section 262 of Title 42, including claims data, patient survey data, standardized analytic files that allow for the pooling and analysis of data from disparate data environments, and any other data deemed appropriate by the Secretary.

(B) Development of postmarket risk identification and analysis methods

The Secretary shall, not later than 2 years after September 27, 2007, in collaboration with public, academic, and private entities--

(i) develop methods to obtain access to disparate data sources including the data sources specified in subparagraph (C);

(ii) develop validated methods for the establishment of a postmarket risk identification and analysis system to link and analyze safety data from multiple sources, with the goals of including, in aggregate--

(I) at least 25,000,000 patients by July 1, 2010; and

(II) at least 100,000,000 patients by July 1, 2012; and

(iii) convene a committee of experts, including individuals who are recognized in the field of protecting data privacy and security, to make recommendations to the Secretary on the development of tools and methods for the ethical and scientific uses for, and communication of, postmarketing data specified under subparagraph (C), including recommendations on the development of effective research methods for the study of drug safety questions.

(C) Establishment of the postmarket risk identification and analysis system

(i) In general

The Secretary shall, not later than 1 year after the development of the risk identification and analysis methods under subparagraph (B), establish and maintain procedures--

(I) for risk identification and analysis based on electronic health data, in compliance with the regulations promulgated under section 264(c) of the Health Insurance Portability and Accountability Act of 1996,

and in a manner that does not disclose individually identifiable health information in violation of paragraph (4)(B);

(II) for the reporting (in a standardized form) of data on all serious adverse drug experiences (as defined in section 355-1(b) of this title) submitted to the Secretary under paragraph (1), and those adverse events submitted by patients, providers, and drug sponsors, when appropriate;

(III) to provide for active adverse event surveillance using the following data sources, as available:

(aa) Federal health-related electronic data (such as data from the Medicare program and the health systems of the Department of Veterans Affairs);

(bb) private sector health-related electronic data (such as pharmaceutical purchase data and health insurance claims data); and

(cc) other data as the Secretary deems necessary to create a robust system to identify adverse events and potential drug safety signals;

(IV) to identify certain trends and patterns with respect to data accessed by the system;

(V) to provide regular reports to the Secretary concerning adverse event trends, adverse event patterns, incidence and prevalence of adverse events, and other information the Secretary determines appropriate, which may include data on comparative national adverse event trends; and

(VI) to enable the program to export data in a form appropriate for further aggregation, statistical analysis, and reporting.

(ii) Timeliness of reporting

The procedures established under clause (i) shall ensure that such data are accessed, analyzed, and reported in a timely, routine, and systematic manner, taking into consideration the need for data completeness, coding, cleansing, and standardized analysis and transmission.

(iii) Private sector resources

To ensure the establishment of the active postmarket risk identification and analysis system under this subsection not later than 1 year after the development of the risk identification and analysis methods under subparagraph (B), as required under clause (i), the Secretary may, on a temporary or permanent basis, implement systems or products developed by private entities.

(iv) Complementary approaches

To the extent the active postmarket risk identification and analysis system under this subsection is not sufficient to gather data and information relevant to a priority drug safety question, the Secretary shall develop, support, and participate in complementary approaches to gather and analyze such data and information, including--

(I) approaches that are complementary with respect to assessing the safety of use of a drug in domestic populations not included, or underrepresented, in the trials used to approve the drug (such as older people, people with comorbidities, pregnant women, or children); and

(II) existing approaches such as the Vaccine Adverse Event Reporting System and the Vaccine Safety Datalink or successor databases.

(v) Authority for contracts

The Secretary may enter into contracts with public and private entities to fulfill the requirements of this subparagraph.

(4) Advanced analysis of drug safety data

(A) Purpose

The Secretary shall establish collaborations with public, academic, and private entities, which may include the Centers for Education and Research on Therapeutics under section 299b-1 of Title 42, to provide for advanced analysis of drug safety data described in paragraph (3)(C) and other information that is publicly available or is provided by the Secretary, in order to--

(i) improve the quality and efficiency of postmarket drug safety risk-benefit analysis;

(ii) provide the Secretary with routine access to outside expertise to study advanced drug safety questions; and

(iii) enhance the ability of the Secretary to make timely assessments based on drug safety data.

(B) Privacy

Such analysis shall not disclose individually identifiable health information when presenting such drug safety signals and trends or when responding to inquiries regarding such drug safety signals and trends.

(C) Public process for priority questions

At least biannually, the Secretary shall seek recommendations from the Drug Safety and Risk Management Advisory Committee (or any successor committee) and from other advisory committees, as appropriate, to the Food and Drug Administration on--

(i) priority drug safety questions; and

(ii) mechanisms for answering such questions, including through--

(I) active risk identification under paragraph (3); and

(II) when such risk identification is not sufficient, postapproval studies and clinical trials under subsection (o)(3) of this section.

(D) Procedures for the development of drug safety collaborations

(i) In general

Not later than 180 days after the date of the establishment of the active postmarket risk identification and analysis system under this subsection, the Secretary shall establish and implement procedures under which the Secretary may routinely contract with one or more qualified entities to--

(I) classify, analyze, or aggregate data described in paragraph (3)(C) and information that is publicly available or is provided by the Secretary;

(II) allow for prompt investigation of priority drug safety questions, including--

(aa) unresolved safety questions for drugs or classes of drugs; and

(bb) for a newly-approved drugs, safety signals from clinical trials used to approve the drug and other preapproval trials; rare, serious drug side effects; and the safety of use in domestic populations not included, or underrepresented, in the trials used to approve the drug (such as older people, people with comorbidities, pregnant women, or children);

(III) perform advanced research and analysis on identified drug safety risks;

(IV) focus postapproval studies and clinical trials under subsection (o)(3) of this section more effectively on cases for which reports under paragraph (1) and other safety signal detection is not sufficient to resolve whether there is an elevated risk of a serious adverse event associated with the use of a drug; and

(V) carry out other activities as the Secretary deems necessary to carry out the purposes of this paragraph.

(ii) Request for specific methodology

The procedures described in clause (i) shall permit the Secretary to request that a specific methodology be used by the qualified entity. The qualified entity shall work with the Secretary to finalize the methodology to be used.

(E) Use of analyses

The Secretary shall provide the analyses described in this paragraph, including the methods and results of such analyses, about a drug to the sponsor or sponsors of such drug.

(F) Qualified entities

(i) In general

The Secretary shall enter into contracts with a sufficient number of qualified entities to develop and provide information to the Secretary in a timely manner.

(ii) Qualification

The Secretary shall enter into a contract with an entity under clause (i) only if the Secretary determines that the entity has a significant presence in the

United States and has one or more of the following qualifications:

(I) The research, statistical, epidemiologic, or clinical capability and expertise to conduct and complete the activities under this paragraph, including the capability and expertise to provide the Secretary de-identified data consistent with the requirements of this subsection.

(II) An information technology infrastructure in place to support electronic data and operational standards to provide security for such data.

(III) Experience with, and expertise on, the development of drug safety and effectiveness research using electronic population data.

(IV) An understanding of drug development or risk/benefit balancing in a clinical setting.

(V) Other expertise which the Secretary deems necessary to fulfill the activities under this paragraph.

(G) Contract requirements

Each contract with a qualified entity under subparagraph (F)(i) shall contain the following requirements:

(i) Ensuring privacy

The qualified entity shall ensure that the entity will not use data under this subsection in a manner that--

(I) violates the regulations promulgated under section 264(c) of the Health Insurance Portability and Accountability Act of 1996;

(II) violates sections 552 or 552a of Title 5 with regard to the privacy of individually-identifiable beneficiary health information; or

(III) discloses individually identifiable health information when presenting drug safety signals and trends or when responding to inquiries regarding drug safety signals and trends.

Nothing in this clause prohibits lawful disclosure for other purposes.

(ii) Component of another organization

If a qualified entity is a component of another organization--

(I) the qualified entity shall establish appropriate security measures to maintain the confidentiality and privacy of such data; and

(II) the entity shall not make an unauthorized disclosure of such data to the other components of the organization in breach of such confidentiality and privacy requirement.

(iii) Termination or nonrenewal

If a contract with a qualified entity under this subparagraph is terminated or not renewed, the following requirements shall apply:

(I) Confidentiality and privacy protections

The entity shall continue to comply with the confidentiality and privacy requirements under this paragraph with respect to all data disclosed to the entity.

(II) Disposition of data

The entity shall return any data disclosed to such entity under this subsection to which it would not otherwise have access or, if returning the data is not practicable, destroy the data.

(H) Competitive procedures

The Secretary shall use competitive procedures (as defined in section 403(5) of Title 41) to enter into contracts under subparagraph (G).

(I) Review of contract in the event of a merger or acquisition

The Secretary shall review the contract with a qualified entity under this paragraph in the event of a merger or acquisition of the entity in order to ensure that the requirements under this paragraph will continue to be met.

(J) Coordination

In carrying out this paragraph, the Secretary shall provide for appropriate communications to the public, scientific, public health, and medical communities, and other key stakeholders, and to the extent practicable shall coordinate with the activities of private entities, professional associations, or other entities that may have sources of drug safety data.

(5) The Secretary shall--

(A) conduct regular, bi-weekly screening of the Adverse Event Reporting System database and post a quarterly report on the Adverse Event Reporting System Web site of any new safety information or potential signal of a serious risk identified by Adverse Event Reporting System within the last quarter;

(B) report to Congress not later than 2 year [FN2] after September 27, 2007 on procedures and processes of the Food and Drug Administration for addressing ongoing post market safety issues identified by the Office of Surveillance and Epidemiology and how recommendations of the Office of Surveillance and Epidemiology are handled within the agency; and

(C) on an annual basis, review the entire backlog of postmarket safety commitments to determine which commitments require revision or should be eliminated, report to the Congress on these determinations, and assign start dates and estimated completion dates for such commitments.

(l) Public disclosure of safety and effectiveness data

(1) Safety and effectiveness data and information which has been submitted in an application under subsection (b) of this section for a drug and which has not previously been disclosed to the public shall be made available to the public, upon request, unless extraordinary circumstances are shown--

(A) if no work is being or will be undertaken to have the application approved,

(B) if the Secretary has determined that the application is not approvable and all legal appeals have been exhausted,

(C) if approval of the application under subsection (c) of this section is withdrawn and all legal appeals have been exhausted,

(D) if the Secretary has determined that such drug is not a new drug, or

(E) upon the effective date of the approval of the first application under subsection (j) of this section which refers to such drug or upon the date upon which the approval of an application under subsection (j) of this section which refers to such drug could be made effective if such an application had been submitted.

(2) Action package for approval

(A) Action package

The Secretary shall publish the action package for approval of an application under subsection (b) of this section or section 262 of title 42 on the Internet Web site of the Food and Drug Administration--

(i) not later than 30 days after the date of approval of such application for a drug no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under this section or section 262 of Title 42; and

(ii) not later than 30 days after the third request for such action package for approval received under section 552 of Title 5 for any other drug.

(B) Immediate publication of summary review

Notwithstanding subparagraph (A), the Secretary shall publish, on the Internet Web site of the Food and Drug Administration, the materials described in subparagraph (C)(iv) not later than 48 hours after the date of approval of the drug, except where such materials require redaction by the Secretary.

(C) Contents

An action package for approval of an application under subparagraph (A) shall be dated and shall include the following:

(i) Documents generated by the Food and Drug Administration related to review of the application.

(ii) Documents pertaining to the format and content of the application generated during drug development.

(iii) Labeling submitted by the applicant.

(iv) A summary review that documents conclusions from all reviewing disciplines about the drug, noting any critical issues and disagreements with the appli-

cant and within the review team and how they were resolved, recommendations for action, and an explanation of any nonconcurrence with review conclusions.

(v) The Division Director and Office Director's decision document which includes--

(I) a brief statement of concurrence with the summary review;

(II) a separate review or addendum to the review if disagreeing with the summary review; and

(III) a separate review or addendum to the review to add further analysis.

(vi) Identification by name of each officer or employee of the Food and Drug Administration who--

(I) participated in the decision to approve the application; and

(II) consents to have his or her name included in the package.

(D) Review

A scientific review of an application is considered the work of the reviewer and shall not be altered by management or the reviewer once final.

(E) Confidential information

This paragraph does not authorize the disclosure of any trade secret, confidential commercial or financial information, or other matter listed in section 552(b) of Title 5.

(m) "Patent" defined

For purposes of this section, the term "patent" means a patent issued by the United States Patent and Trademark Office.

(n) Scientific advisory panels

(1) For the purpose of providing expert scientific advice and recommendations to the Secretary regarding a clinical investigation of a drug or the approval for marketing of a drug under this section or section 262 of Title 42, the Secretary shall establish panels of experts or use panels of experts established before November 21, 1997, or both.

(2) The Secretary may delegate the appointment and oversight authority granted under section 394 of this title to a director of a center or successor entity within the Food and Drug Administration.

(3) The Secretary shall make appointments to each panel established under paragraph (1) so that each panel shall consist of--

(A) members who are qualified by training and experience to evaluate the safety and effectiveness of the drugs to be referred to the panel and who, to the extent feasible, possess skill and experience in the development, manufacture, or utilization of such drugs;

(B) members with diverse expertise in such fields as clinical and administrative medicine, pharmacy, pharmacology, pharmacoeconomics, biological and physical sciences, and other related professions;

(C) a representative of consumer interests, and a representative of interests of the drug manufacturing industry not directly affected by the matter to be brought before the panel; and

(D) two or more members who are specialists or have other expertise in the particular disease or condition for which the drug under review is proposed to be indicated.

Scientific, trade, and consumer organizations shall be afforded an opportunity to nominate individuals for appointment to the panels. No individual who is in the regular full-time employ of the United States and engaged in the administration of this chapter may be a voting member of any panel. The Secretary shall designate one of the members of each panel to serve as chairman thereof.

(4) The Secretary shall, as appropriate, provide education and training to each new panel member before such member participates in a panel's activities, including education regarding requirements under this chapter and related regulations of the Secretary, and the administrative processes and procedures related to panel meetings.

(5) Panel members (other than officers or employees of the United States), while attending meetings or conferences of a panel or otherwise engaged in its business, shall be entitled to receive compensation for each day so engaged, including traveltime, at rates to be fixed by the Secretary, but not to exceed the daily equivalent of the rate in effect for positions classified above grade GS-15 of the General Schedule. While serving away from their homes or regular places of business, panel members may be allowed travel expenses (including per diem in lieu of subsistence) as authorized by section 5703 of Title 5, for persons in the Government service employed intermittently.

(6) The Secretary shall ensure that scientific advisory panels meet regularly and at appropriate intervals so

that any matter to be reviewed by such a panel can be presented to the panel not more than 60 days after the matter is ready for such review. Meetings of the panel may be held using electronic communication to convene the meetings.

(7) Within 90 days after a scientific advisory panel makes recommendations on any matter under its review, the Food and Drug Administration official responsible for the matter shall review the conclusions and recommendations of the panel, and notify the affected persons of the final decision on the matter, or of the reasons that no such decision has been reached. Each such final decision shall be documented including the rationale for the decision.

(8) Redesignated (7)

(o) Postmarket studies and clinical trials; labeling

(1) In general

A responsible person may not introduce or deliver for introduction into interstate commerce the new drug involved if the person is in violation of a requirement established under paragraph (3) or (4) with respect to the drug.

(2) Definitions

For purposes of this subsection:

(A) Responsible person

The term "responsible person" means a person who--

(i) has submitted to the Secretary a covered application that is pending; or

(ii) is the holder of an approved covered application.

(B) Covered application

The term "covered application" means--

(i) an application under subsection (b) of this section for a drug that is subject to section 353(b) of this title; and

(ii) an application under section 262 of Title 42.

(C) New safety information; serious risk

The terms "new safety information", "serious risk", and "signal of a serious risk" have the meanings given such terms in section 355-1(b) of this title.

(3) Studies and clinical trials

(A) In general

For any or all of the purposes specified in subparagraph (B), the Secretary may, subject to subparagraph (D), require a responsible person for a drug to conduct a postapproval study or studies of the drug, or a postapproval clinical trial or trials of the drug, on the basis of scientific data deemed appropriate by the Secretary, including information regarding chemically-related or pharmacologically-related drugs.

(B) Purposes of study or clinical trial

The purposes referred to in this subparagraph with respect to a postapproval study or postapproval clinical trial are the following:

(i) To assess a known serious risk related to the use of the drug involved.

(ii) To assess signals of serious risk related to the use of the drug.

(iii) To identify an unexpected serious risk when available data indicates the potential for a serious risk.

(C) Establishment of requirement after approval of covered application

The Secretary may require a postapproval study or studies or postapproval clinical trial or trials for a drug for which an approved covered application is in effect as of the date on which the Secretary seeks to establish such requirement only if the Secretary becomes aware of new safety information.

(D) Determination by Secretary

(i) Postapproval studies

The Secretary may not require the responsible person to conduct a study under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) of this section and the active postmarket risk identification and analysis system as available under subsection (k)(3) of this section will not be sufficient to meet the purposes set forth in subparagraph (B).

(ii) Postapproval clinical trials

The Secretary may not require the responsible person to conduct a clinical trial under this paragraph, unless the Secretary makes a determination that a postapproval study or studies will not be sufficient to meet the purposes set forth in subparagraph (B).

(E) Notification; timetables; periodic reports

(i) Notification

The Secretary shall notify the responsible person regarding a requirement under this paragraph to conduct a postapproval study or clinical trial by the target dates for communication of feedback from the review team to the responsible person regarding proposed labeling and postmarketing study commit-

ments as set forth in the letters described in section 101(c) of the Food and Drug Administration Amendments Act of 2007.

(ii) Timetable; periodic reports

For each study or clinical trial required to be conducted under this paragraph, the Secretary shall require that the responsible person submit a timetable for completion of the study or clinical trial. With respect to each study required to be conducted under this paragraph or otherwise undertaken by the responsible person to investigate a safety issue, the Secretary shall require the responsible person to periodically report to the Secretary on the status of such study including whether any difficulties in completing the study have been encountered. With respect to each clinical trial required to be conducted under this paragraph or otherwise undertaken by the responsible person to investigate a safety issue, the Secretary shall require the responsible person to periodically report to the Secretary on the status of such clinical trial including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to the requirements under section 282(j) of Title 42. If the responsible person fails to comply with such timetable or violates any other requirement of this subparagraph, the responsible person shall be considered in violation of this subsection, unless the responsible person demonstrates good cause for such noncompliance or such other violation. The Secretary shall determine what constitutes good cause under the preceding sentence.

(F) Dispute resolution

The responsible person may appeal a requirement to conduct a study or clinical trial under this paragraph using dispute resolution procedures established by the Secretary in regulation and guidance.

(4) Safety labeling changes requested by Secretary

(A) New safety information

If the Secretary becomes aware of new safety information that the Secretary believes should be included in the labeling of the drug, the Secretary shall promptly notify the responsible person or, if the same drug approved under subsection (b) of this section is not currently marketed, the holder of an approved application under subsection (j) of this section.

(B) Response to notification

Following notification pursuant to subparagraph (A), the responsible person or the holder of the approved application under subsection (j) of this section shall within 30 days--

(i) submit a supplement proposing changes to the approved labeling to reflect the new safety information, including changes to boxed warnings, contraindications, warnings, precautions, or adverse reactions; or

(ii) notify the Secretary that the responsible person or the holder of the approved application under subsection (j) of this section does not believe a labeling change is warranted and submit a statement detailing the reasons why such a change is not warranted.

(C) Review

Upon receipt of such supplement, the Secretary shall promptly review and act upon such supplement. If the Secretary disagrees with the proposed changes in the supplement or with the statement setting forth

the reasons why no labeling change is necessary, the Secretary shall initiate discussions to reach agreement on whether the labeling for the drug should be modified to reflect the new safety information, and if so, the contents of such labeling changes.

(D) Discussions

Such discussions shall not extend for more than 30 days after the response to the notification under subparagraph (B), unless the Secretary determines an extension of such discussion period is warranted.

(E) Order

Within 15 days of the conclusion of the discussions under subparagraph (D), the Secretary may issue an order directing the responsible person or the holder of the approved application under subsection (j) of this section to make such a labeling change as the Secretary deems appropriate to address the new safety information. Within 15 days of such an order, the responsible person or the holder of the approved application under subsection (j) of this section shall submit a supplement containing the labeling change.

(F) Dispute resolution

Within 5 days of receiving an order under subparagraph (E), the responsible person or the holder of the approved application under subsection (j) of this section may appeal using dispute resolution procedures established by the Secretary in regulation and guidance.

(G) Violation

If the responsible person or the holder of the approved application under subsection (j) of this section has not submitted a supplement within 15 days of the

date of such order under subparagraph (E), and there is no appeal or dispute resolution proceeding pending, the responsible person or holder shall be considered to be in violation of this subsection. If at the conclusion of any dispute resolution procedures the Secretary determines that a supplement must be submitted and such a supplement is not submitted within 15 days of the date of that determination, the responsible person or holder shall be in violation of this subsection.

(H) Public health threat

Notwithstanding subparagraphs (A) through (F), if the Secretary concludes that such a labeling change is necessary to protect the public health, the Secretary may accelerate the timelines in such subparagraphs.

(I) Rule of construction

This paragraph shall not be construed to affect the responsibility of the responsible person or the holder of the approved application under subsection (j) of this section to maintain its label in accordance with existing requirements, including subpart B of part 201 and sections 314.70 and 601.12 of title 21, Code of Federal Regulations (or any successor regulations).

(5) Non-delegation

Determinations by the Secretary under this subsection for a drug shall be made by individuals at or above the level of individuals empowered to approve a drug (such as division directors within the Center for Drug Evaluation and Research).

(p) Risk evaluation and mitigation strategy

(1) In general

A person may not introduce or deliver for introduction into interstate commerce a new drug if--

(A)(i) the application for such drug is approved under subsection (b) or (j) of this section and is subject to section 353(b) of this title; or

(ii) the application for such drug is approved under section 262 of Title 42; and

(B) a risk evaluation and mitigation strategy is required under section 355-1 of this title with respect to the drug and the person fails to maintain compliance with the requirements of the approved strategy or with other requirements under section 355-1 of this title, including requirements regarding assessments of approved strategies.

(2) Certain postmarket studies

The failure to conduct a postmarket study under section 356 of this title, subpart H of part 314, or subpart E of part 601 of title 21, Code of Federal Regulations (or any successor regulations), is deemed to be a violation of paragraph (1).

(q) Petitions and civil actions regarding approval of certain applications

(1) In general

(A) Determination

The Secretary shall not delay approval of a pending application submitted under subsection (b)(2) or (j) of this section because of any request to take any form of action relating to the application, either before or during consideration of the request, unless--

(i) the request is in writing and is a petition submitted to the Secretary pursuant to section 10.30 or

10.35 of title 21, Code of Federal Regulations (or any successor regulations); and

(ii) the Secretary determines, upon reviewing the petition, that a delay is necessary to protect the public health.

Consideration of the petition shall be separate and apart from review and approval of any application.

(B) Notification

If the Secretary determines under subparagraph (A) that a delay is necessary with respect to an application, the Secretary shall provide to the applicant, not later than 30 days after making such determination, the following information:

(i) Notification of the fact that a determination under subparagraph (A) has been made.

(ii) If applicable, any clarification or additional data that the applicant should submit to the docket on the petition to allow the Secretary to review the petition promptly.

(iii) A brief summary of the specific substantive issues raised in the petition which form the basis of the determination.

(C) Format

The information described in subparagraph (B) shall be conveyed via either, at the discretion of the Secretary--

(i) a document; or

(ii) a meeting with the applicant involved.

(D) Public disclosure

Any information conveyed by the Secretary under subparagraph (C) shall be considered part of the application and shall be subject to the disclosure requirements applicable to information in such application.

(E) Denial based on intent to delay

If the Secretary determines that a petition or a supplement to the petition was submitted with the primary purpose of delaying the approval of an application and the petition does not on its face raise valid scientific or regulatory issues, the Secretary may deny the petition at any point based on such determination. The Secretary may issue guidance to describe the factors that will be used to determine under this subparagraph whether a petition is submitted with the primary purpose of delaying the approval of an application.

(F) Final agency action

The Secretary shall take final agency action on a petition not later than 180 days after the date on which the petition is submitted. The Secretary shall not extend such period for any reason, including--

(i) any determination made under subparagraph (A);

(ii) the submission of comments relating to the petition or supplemental information supplied by the petitioner; or

(iii) the consent of the petitioner.

(G) Extension of 30-month period

If the filing of an application resulted in first-applicant status under subsection (j)(5)(D)(i)(IV) of this section and approval of the application was delayed because of a petition, the 30-month period un-

der such subsection is deemed to be extended by a period of time equal to the period beginning on the date on which the Secretary received the petition and ending on the date of final agency action on the petition (inclusive of such beginning and ending dates), without regard to whether the Secretary grants, in whole or in part, or denies, in whole or in part, the petition.

(H) Certification

The Secretary shall not consider a petition for review unless the party submitting such petition does so in written form and the subject document is signed and contains the following certification: "I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: _____. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: _____. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.", with the date on which such information first became known to such party and the names of such persons or organizations inserted in the first and second blank space, respectively.

(I) Verification

The Secretary shall not accept for review any supplemental information or comments on a petition unless the party submitting such information or comments does so in written form and the subject document is signed and contains the following verification: "I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about _____. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: _____. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.", with the date on which such information first became known to the party and the names of such persons or organizations inserted in the first and second blank space, respectively.

(2) Exhaustion of administrative remedies

(A) Final agency action within 180 days

The Secretary shall be considered to have taken final agency action on a petition if--

(i) during the 180-day period referred to in paragraph (1)(F), the Secretary makes a final decision within the meaning of section 10.45(d) of title 21, Code of Federal Regulations (or any successor regulation); or

(ii) such period expires without the Secretary having made such a final decision.

(B) Dismissal of certain civil actions

If a civil action is filed against the Secretary with respect to any issue raised in the petition before the Secretary has taken final agency action on the petition within the meaning of subparagraph (A), the court shall dismiss without prejudice the action for failure to exhaust administrative remedies.

(C) Administrative record

For purposes of judicial review related to the approval of an application for which a petition under paragraph (1) was submitted, the administrative record regarding any issue raised by the petition shall include--

(i) the petition filed under paragraph (1) and any supplements and comments thereto;

(ii) the Secretary's response to such petition, if issued; and

(iii) other information, as designated by the Secretary, related to the Secretary's determinations regarding the issues raised in such petition, as long as the information was considered by the agency no later than the date of final agency action as defined under subparagraph (2)(A), and regardless of whether the Secretary responded to the petition at or before the approval of the application at issue in the petition.

(3) Annual report on delays in approvals per petitions

The Secretary shall annually submit to the Congress a report that specifies--

(A) the number of applications that were approved during the preceding 12-month period;

(B) the number of such applications whose effective dates were delayed by petitions referred to in paragraph (1) during such period;

(C) the number of days by which such applications were so delayed; and

(D) the number of such petitions that were submitted during such period.

(4) Exceptions

This subsection does not apply to--

(A) a petition that relates solely to the timing of the approval of an application pursuant to subsection (j)(5)(B)(iv) of this section; or

(B) a petition that is made by the sponsor of an application and that seeks only to have the Secretary take or refrain from taking any form of action with respect to that application.

(5) Definitions

(A) Application

For purposes of this subsection, the term "application" means an application submitted under subsection (b)(2) or (j) of this section.

(B) Petition

For purposes of this subsection, other than paragraph (1)(A)(i), the term "petition" means a request described in paragraph (1)(A)(i).

(r) Postmarket drug safety information for patients and providers

(1) Establishment

Not later than 1 year after September 27, 2007, the Secretary shall improve the transparency of informa-

tion about drugs and allow patients and health care providers better access to information about drugs by developing and maintaining an Internet Web site that--

(A) provides links to drug safety information listed in paragraph (2) for prescription drugs that are approved under this section or licensed under section 262 of Title 42; and

(B) improves communication of drug safety information to patients and providers.

(2) Internet Web site

The Secretary shall carry out paragraph (1) by--

(A) developing and maintaining an accessible, consolidated Internet Web site with easily searchable drug safety information, including the information found on United States Government Internet Web sites, such as the United States National Library of Medicine's Daily Med and Medline Plus Web sites, in addition to other such Web sites maintained by the Secretary;

(B) ensuring that the information provided on the Internet Web site is comprehensive and includes, when available and appropriate--

(i) patient labeling and patient packaging inserts;

(ii) a link to a list of each drug, whether approved under this section or licensed under such section 262, for which a Medication Guide, as provided for under part 208 of title 21, Code of Federal Regulations (or any successor regulations), is required;

(iii) a link to the registry and results data bank provided for under subsections (i) and (j) of section 282 of Title 42;

(iv) the most recent safety information and alerts issued by the Food and Drug Administration for drugs approved by the Secretary under this section, such as product recalls, warning letters, and import alerts;

(v) publicly available information about implemented RiskMAPs and risk evaluation and mitigation strategies under subsection (o) of this section;

(vi) guidance documents and regulations related to drug safety; and

(vii) other material determined appropriate by the Secretary;

(C) providing access to summaries of the assessed and aggregated data collected from the active surveillance infrastructure under subsection (k)(3) of this section to provide information of known and serious side-effects for drugs approved under this section or licensed under such section 262 of Title 42;

(D) preparing, by 18 months after approval of a drug or after use of the drug by 10,000 individuals, whichever is later, a summary analysis of the adverse drug reaction reports received for the drug, including identification of any new risks not previously identified, potential new risks, or known risks reported in unusual number;

(E) enabling patients, providers, and drug sponsors to submit adverse event reports through the Internet Web site;

(F) providing educational materials for patients and providers about the appropriate means of disposing of expired, damaged, or unusable medications; and

(G) supporting initiatives that the Secretary determines to be useful to fulfill the purposes of the Internet Web site.

(3) Posting of drug labeling

The Secretary shall post on the Internet Web site established under paragraph (1) the approved professional labeling and any required patient labeling of a drug approved under this section or licensed under such section 262 of Title 42 not later than 21 days after the date the drug is approved or licensed, including in a supplemental application with respect to a labeling change.

(4) Private sector resources

To ensure development of the Internet Web site by the date described in paragraph (1), the Secretary may, on a temporary or permanent basis, implement systems or products developed by private entities.

(5) Authority for contracts

The Secretary may enter into contracts with public and private entities to fulfill the requirements of this subsection.

(6) Review

The Advisory Committee on Risk Communication under section 360bbb-6 of this title shall, on a regular basis, perform a comprehensive review and evaluation of the types of risk communication information provided on the Internet Web site established under paragraph (1) and, through other means, shall identify, clarify, and define the purposes and types of information available to facilitate the efficient flow of information to patients and providers, and shall recommend ways for the Food and Drug Administration

to work with outside entities to help facilitate the dispensing of risk communication information to patients and providers.

(s) Referral to advisory committee

Prior to the approval of a drug no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under this section or section 262 of Title 42, the Secretary shall--

(1) refer such drug to a Food and Drug Administration advisory committee for review at a meeting of such advisory committee; or

(2) if the Secretary does not refer such a drug to a Food and Drug Administration advisory committee prior to the approval of the drug, provide in the action letter on the application for the drug a summary of the reasons why the Secretary did not refer the drug to an advisory committee prior to approval.

(t) Database for authorized generic drugs

(1) In general

(A) Publication

The Commissioner shall--

(i) not later than 9 months after September 27, 2007, publish a complete list on the Internet Web site of the Food and Drug Administration of all authorized generic drugs (including drug trade name, brand company manufacturer, and the date the authorized generic drug entered the market); and

(ii) update the list quarterly to include each authorized generic drug included in an annual report submitted to the Secretary by the sponsor of a listed drug during the preceding 3-month period.

(B) Notification

The Commissioner shall notify relevant Federal agencies, including the Centers for Medicare & Medicaid Services and the Federal Trade Commission, when the Commissioner first publishes the information described in subparagraph (A) that the information has been published and that the information will be updated quarterly.

(2) Inclusion

The Commissioner shall include in the list described in paragraph (1) each authorized generic drug included in an annual report submitted to the Secretary by the sponsor of a listed drug after January 1, 1999.

(3) Authorized generic drug

In this section, the term "authorized generic drug" means a listed drug (as that term is used in subsection (j) of this section) that--

(A) has been approved under subsection (c) of this section; and

(B) is marketed, sold, or distributed directly or indirectly to retail class of trade under a different labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trade mark than the listed drug.

(u) Certain drugs containing single enantiomers

(1) In general

For purposes of subsections (c)(3)(E)(ii) and (j)(5)(F)(ii) of this section, if an application is submitted under subsection (b) of this section for a nonracemic drug containing as an active ingredient (in-

cluding any ester or salt of the active ingredient) a single enantiomer that is contained in a racemic drug approved in another application under subsection (b) of this section, the applicant may, in the application for such non-racemic drug, elect to have the single enantiomer not be considered the same active ingredient as that contained in the approved racemic drug, if--

(A)(i) the single enantiomer has not been previously approved except in the approved racemic drug; and

(ii) the application submitted under subsection (b) of this section for such non-racemic drug--

(I) includes full reports of new clinical investigations (other than bioavailability studies)--

(aa) necessary for the approval of the application under subsections (c) and (d) of this section; and

(bb) conducted or sponsored by the applicant; and

(II) does not rely on any investigations that are part of an application submitted under subsection (b) of this section for approval of the approved racemic drug; and

(B) the application submitted under subsection (b) of this section for such non-racemic drug is not submitted for approval of a condition of use--

(i) in a therapeutic category in which the approved racemic drug has been approved; or

(ii) for which any other enantiomer of the racemic drug has been approved.

(2) Limitation

(A) No approval in certain therapeutic categories

Until the date that is 10 years after the date of approval of a non-racemic drug described in paragraph (1) and with respect to which the applicant has made the election provided for by such paragraph, the Secretary shall not approve such non-racemic drug for any condition of use in the therapeutic category in which the racemic drug has been approved.

(B) Labeling

If applicable, the labeling of a non-racemic drug described in paragraph (1) and with respect to which the applicant has made the election provided for by such paragraph shall include a statement that the non-racemic drug is not approved, and has not been shown to be safe and effective, for any condition of use of the racemic drug.

(3) Definition

(A) In general

For purposes of this subsection, the term "therapeutic category" means a therapeutic category identified in the list developed by the United States Pharmacopeia pursuant to section 1395w-104(b)(3)(C)(ii) of Title 42 and as in effect on September 27, 2007.

(B) Publication by Secretary

The Secretary shall publish the list described in subparagraph (A) and may amend such list by regulation.

(4) Availability

The election referred to in paragraph (1) may be made only in an application that is submitted to the Secretary after September 27, 2007, and before October 1, 2012.

(v) Antibiotic drugs submitted before November 21, 1997

(1) Antibiotic drugs approved before November 21, 1997

(A) In general

Notwithstanding any provision of the Food and Drug Administration Modernization Act of 1997 or any other provision of law, a sponsor of a drug that is the subject of an application described in subparagraph (B)(i) shall be eligible for, with respect to the drug, the 3-year exclusivity period referred to under clauses (iii) and (iv) of subsection (c)(3)(E) and under clauses (iii) and (iv) of subsection (j)(5)(F), subject to the requirements of such clauses, as applicable.

(B) Application; antibiotic drug described

(i) Application

An application described in this clause is an application for marketing submitted under this section after October 8, 2008 in which the drug that is the subject of the application contains an antibiotic drug described in clause (ii).

(ii) Antibiotic drug

An antibiotic drug described in this clause is an antibiotic drug that was the subject of an application approved by the Secretary under section 357 of this title (as in effect before November 21, 1997).

(2) Antibiotic drugs submitted before November 21, 1997, but not approved

(A) In general

Notwithstanding any provision of the Food and Drug Administration Modernization Act of 1997 or any

other provision of law, a sponsor of a drug that is the subject of an application described in subparagraph (B)(i) may elect to be eligible for, with respect to the drug--

(i)(I) the 3-year exclusivity period referred to under clauses (iii) and (iv) of subsection (c)(3)(E) and under clauses (iii) and (iv) of subsection (j)(5)(F), subject to the requirements of such clauses, as applicable; and

(II) the 5-year exclusivity period referred to under clause (ii) of subsection (c)(3)(E) and under clause (ii) of subsection (j)(5)(F), subject to the requirements of such clauses, as applicable; or

(ii) a patent term extension under section 156 of Title 35 subject to the requirements of such section.

(B) Application; antibiotic drug described

(i) Application

An application described in this clause is an application for marketing submitted under this section after October 8, 2008 in which the drug that is the subject of the application contains an antibiotic drug described in clause (ii).

(ii) Antibiotic drug

An antibiotic drug described in this clause is an antibiotic drug that was the subject of 1 or more applications received by the Secretary under section 357 of this title (as in effect before November 21, 1997), none of which was approved by the Secretary under such section.

(3) Limitations

(A) Exclusivities and extensions

Paragraphs (1)(A) and (2)(A) shall not be construed to entitle a drug that is the subject of an approved application described in subparagraphs (1)(B)(i) or (2)(B)(i), as applicable, to any market exclusivities or patent extensions other than those exclusivities or extensions described in paragraph (1)(A) or (2)(A).

(B) Conditions of use

Paragraphs (1)(A) and (2)(A)(i) shall not apply to any condition of use for which the drug referred to in subparagraph (1)(B)(i) or (2)(B)(i), as applicable, was approved before October 8, 2008.

(4) Application of certain provisions

Notwithstanding section 125, or any other provision, of the Food and Drug Administration Modernization Act of 1997, or any other provision of law, and subject to the limitations in paragraphs (1), (2), and (3), the provisions of the Drug Price Competition and Patent Term Restoration Act of 1984 shall apply to any drug subject to paragraph (1) or any drug with respect to which an election is made under paragraph (2)(A).

APPDENDIX G

CODE OF FEDERAL REGULATIONS

TITLE 21—FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED)

Part 314. Applications for FDA Approval to Market a New Drug--

Table of Contents

Subpart B. Applications

Sec. 314.53 Submission of patent information.

(a) Who must submit patent information. This section applies to any applicant who submits to FDA a new drug application or an amendment to it under section 505(b) of the act and § 314.50 or a supplement to an approved application under § 314.70, except as provided in paragraph (d)(2) of this section.

(b) Patents for which information must be submitted and patents for which information must not be submitted--

(1) General requirements. An applicant described in paragraph (a) of this section shall submit the required information on the declaration form set forth in paragraph (c) of this section for each patent that claims the drug or a method of using the drug that is the subject of the new drug application or amendment or supplement to it and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. For purposes of this part, such patents consist of drug

substance (active ingredient) patents, drug product (formulation and composition) patents, and method-of-use patents. For patents that claim the drug substance, the applicant shall submit information only on those patents that claim the drug substance that is the subject of the pending or approved application or that claim a drug substance that is the same as the active ingredient that is the subject of the approved or pending application. For patents that claim a polymorph that is the same as the active ingredient described in the approved or pending application, the applicant shall certify in the declaration forms that the applicant has test data, as set forth in paragraph (b)(2) of this section, demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the new drug application. For patents that claim a drug product, the applicant shall submit information only on those patents that claim a drug product, as is defined in § 314.3, that is described in the pending or approved application. For patents that claim a method of use, the applicant shall submit information only on those patents that claim indications or other conditions of use that are described in the pending or approved application. The applicant shall separately identify each pending or approved method of use and related patent claim. For approved applications, the applicant submitting the method-of-use patent shall identify with specificity the section of the approved labeling that corresponds to the method of use claimed by the patent submitted. Process patents, patents claiming packaging, patents claiming metabolites, and patents claiming intermediates are not covered by

this section, and information on these patents must not be submitted to FDA.

(2) Test Data for Submission of Patent Information for Patents That Claim a Polymorph. The test data, referenced in paragraph (b)(1) of this section, must include the following:

(i) A full description of the polymorphic form of the drug substance, including its physical and chemical characteristics and stability; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and such specifications and analytical methods as are necessary to assure the identity, strength, quality, and purity of the polymorphic form of the drug substance;

(ii) The executed batch record for a drug product containing the polymorphic form of the drug substance and documentation that the batch was manufactured under current good manufacturing practice requirements;

(iii) Demonstration of bioequivalence between the executed batch of the drug product that contains the polymorphic form of the drug substance and the drug product as described in the NDA;

(iv) A list of all components used in the manufacture of the drug product containing the polymorphic form and a statement of the composition of the drug product; a statement of the specifications and analytical methods for each component; a description of the manufacturing and packaging procedures and in-process controls for the drug product; such specifications and analytical methods as are necessary to assure the identity, strength, quality, purity, and bioavailability of the drug

product, including release and stability data complying with the approved product specifications to demonstrate pharmaceutical equivalence and comparable product stability; and

(v) Comparative in vitro dissolution testing on 12 dosage units each of the executed test batch and the new drug application product.

(c) Reporting requirements--

(1) General requirements. An applicant described in paragraph (a) of this section shall submit the required patent information described in paragraph (c)(2) of this section for each patent that meets the requirements described in paragraph (b) of this section. We will not accept the patent information unless it is complete and submitted on the appropriate forms, FDA Forms 3542 or 3542a. These forms may be obtained on the Internet at http://www.fda.gov by searching for "forms".

(2) Drug substance (active ingredient), drug product (formulation or composition), and method-of-use patents--

(i) Original Declaration. For each patent that claims a drug substance (active ingredient), drug product (formulation and composition), or method of use, the applicant shall submit FDA Form 3542a. The following information and verification is required:

(A) New drug application number;

(B) Name of new drug application sponsor;

(C) Trade name (or proposed trade name) of new drug;

(D) Active ingredient(s) of new drug;

(E) Strength(s) of new drug;

(F) Dosage form of new drug;

(G) United States patent number, issue date, and expiration date of patent submitted;

(H) The patent owner's name, full address, phone number and, if available, fax number and e-mail address;

(I) The name, full address, phone number and, if available, fax number and e-mail address of an agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under sections 505(b)(3) and 505(j)(2)(B) of the act and §§ 314.52 and 314.95 (if patent owner or new drug application applicant or holder does not reside or have a place of business within the United States);

(J) Information on whether the patent has been submitted previously for the new drug application;

(K) Information on whether the expiration date is a new expiration date if the patent had been submitted previously for listing;

(L) Information on whether the patent is a product-by-process patent in which the product claimed is novel;

(M) Information on the drug substance (active ingredient) patent including the following:

(1) Whether the patent claims the drug substance that is the active ingredient in the drug product described in the new drug application or supplement;

(2) Whether the patent claims a polymorph that is the same active ingredient that is described in the pending application or supplement;

(3) Whether the applicant has test data, described in paragraph (b)(2) of this section, demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the new drug application or supplement, and a description of the polymorphic form(s) claimed by the patent for which such test data exist;

(4) Whether the patent claims only a metabolite of the active ingredient; and

(5) Whether the patent claims only an intermediate;

(N) Information on the drug product (composition/formulation) patent including the following:

(1) Whether the patent claims the drug product for which approval is being sought, as defined in § 314.3; and

(2) Whether the patent claims only an intermediate;

(O) Information on each method-of-use patent including the following:

(1) Whether the patent claims one or more methods of using the drug product for which use approval is being sought and a description of each pending method of use or related indication and related patent claim of the patent being submitted; and

(2) Identification of the specific section of the proposed labeling for the drug product that corresponds to the method of use claimed by the patent submitted;

(P) Whether there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product;

(Q) A signed verification which states: "The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct."; and

(R) Information on whether the applicant, patent owner or attorney, agent, representative or other authorized official signed the form; the name of the person; and the full address, phone number and, if available, the fax number and e-mail address.

(ii) Submission of patent information upon and after approval. Within 30 days after the date of approval of its application or supplement, the appli-

cant shall submit FDA Form 3542 for each patent that claims the drug substance (active ingredient), drug product (formulation and composition), or approved method of use. FDA will rely only on the information submitted on this form and will not list or publish patent information if the patent declaration is incomplete or indicates the patent is not eligible for listing. Patent information must also be submitted for patents issued after the date of approval of the new drug application as required in paragraph (c)(2)(ii) of this section. As described in paragraph (d)(4) of this section, patent information must be submitted to FDA within 30 days of the date of issuance of the patent. If the applicant submits the required patent information within the 30 days, but we notify an applicant that a declaration form is incomplete or shows that the patent is not eligible for listing, the applicant must submit an acceptable declaration form within 15 days of FDA notification to be considered timely filed. The following information and verification statement is required:

(A) New drug application number;

(B) Name of new drug application sponsor;

(C) Trade name of new drug;

(D) Active ingredient(s) of new drug;

(E) Strength(s) of new drug;

(F) Dosage form of new drug;

(G) Approval date of new drug application or supplement;

(H) United States patent number, issue date, and expiration date of patent submitted;

(I) The patent owner's name, full address, phone number and, if available, fax number and e-mail address;

(J) The name, full address, phone number and, if available, fax number and e-mail address of an agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under sections 505(b)(3) and 505(j)(2)(B) of the act and §§ 314.52 and 314.95 (if patent owner or new drug application applicant or holder does not reside or have a place of business within the United States);

(K) Information on whether the patent has been submitted previously for the new drug application;

(L) Information on whether the expiration date is a new expiration date if the patent had been submitted previously for listing;

(M) Information on whether the patent is a product-by-process patent in which the product claimed is novel;

(N) Information on the drug substance (active ingredient) patent including the following:

(1) Whether the patent claims the drug substance that is the active ingredient in the drug product described in the approved application;

(2) Whether the patent claims a polymorph that is the same as the active ingredient that is described in the approved application;

(3) Whether the applicant has test data, described at paragraph (b)(2) of this section, demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the approved application and a description of the polymorphic form(s) claimed by the patent for which such test data exist;

(4) Whether the patent claims only a metabolite of the active ingredient; and

(5) Whether the patent claims only an intermediate;

(O) Information on the drug product (composition/formulation) patent including the following:

(1) Whether the patent claims the approved drug product as defined in § 314.3; and

(2) Whether the patent claims only an intermediate;

(P) Information on each method-of-use patent including the following:

(1) Whether the patent claims one or more approved methods of using the approved drug product and a description of each approved method of use or indication and related patent claim of the patent being submitted;

(2) Identification of the specific section of the approved labeling for the drug product that corresponds to the method of use claimed by the patent submitted; and

(3) The description of the patented method of use as required for publication;

(Q) Whether there are no relevant patents that claim the approved drug substance (active ingredient), the approved drug product (formulation or composition) or approved method(s) of use and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product;

(R) A signed verification which states: "The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct."; and

(S) Information on whether the applicant, patent owner or attorney, agent, representative or other authorized official signed the form; the name of the person; and the full address, phone number and, if available, the fax number and e-mail address.

(3) No relevant patents. If the applicant believes that there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition), or the method(s) of use for which the applicant has received approval,

and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product, the applicant will verify this information in the appropriate forms, FDA Forms 3542 or 3542a.

(4) Authorized signature. The declarations required by this section shall be signed by the applicant or patent owner, or the applicant's or patent owner's attorney, agent (representative), or other authorized official.

(d) When and where to submit patent information--

(1) Original application. An applicant shall submit with its original application submitted under this part, including an application described in section 505(b)(2) of the act, the information described in paragraph (c) of this section on each drug (ingredient), drug product (formulation and composition), and method of use patent issued before the application is filed with FDA and for which patent information is required to be submitted under this section. If a patent is issued after the application is filed with FDA but before the application is approved, the applicant shall, within 30 days of the date of issuance of the patent, submit the required patent information in an amendment to the application under § 314.60.

(2) Supplements.

(i) An applicant shall submit patent information required under paragraph (c) of this section for a patent that claims the drug, drug product, or method of use for which approval is sought in any of the following supplements:

(A) To change the formulation;

(B) To add a new indication or other condition of use, including a change in route of administration;

(C) To change the strength;

(D) To make any other patented change regarding the drug, drug product, or any method of use.

(ii) If the applicant submits a supplement for one of the changes listed under paragraph (d)(2)(i) of this section and existing patents for which information has already been submitted to FDA claim the changed product, the applicant shall submit a certification with the supplement identifying the patents that claim the changed product.

(iii) If the applicant submits a supplement for one of the changes listed under paragraph (d)(2)(i) of this section and no patents, including previously submitted patents, claim the changed product, it shall so certify.

(iv) The applicant shall comply with the requirements for amendment of formulation or composition and method of use patent information under paragraphs (c)(2)(ii) and (d)(3) of this section.

(3) Patent information deadline. If a patent is issued for a drug, drug product, or method of use after an application is approved, the applicant shall submit to FDA the required patent information within 30 days of the date of issuance of the patent.

(4) Copies. The applicant shall submit two copies of each submission of patent information, an ar-

chival copy and a copy for the chemistry, manufacturing, and controls section of the review copy, to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266. The applicant shall submit the patent information by letter separate from, but at the same time as, submission of the supplement.

(5) Submission date. Patent information shall be considered to be submitted to FDA as of the date the information is received by the Central Document Room.

(6) Identification. Each submission of patent information, except information submitted with an original application, and its mailing cover shall bear prominent identification as to its contents, i.e., "Patent Information," or, if submitted after approval of an application, "Time Sensitive Patent Information."

(e) Public disclosure of patent information. FDA will publish in the list the patent number and expiration date of each patent that is required to be, and is, submitted to FDA by an applicant, and for each use patent, the approved indications or other conditions of use covered by a patent. FDA will publish such patent information upon approval of the application, or, if the patent information is submitted by the applicant after approval of an application as provided under paragraph (d)(2) of this section, as soon as possible after the submission to the agency of the patent information. Patent information submitted by the last working day of a month will be published in that month's supplement to the list. Patent information received by the agency between monthly publication

of supplements to the list will be placed on public display in FDA's Freedom of Information Staff. A request for copies of the file shall be sent in writing to the Freedom of Information Staff (HFI-35), Food and Drug Administration, rm. 12A-16, 5600 Fishers Lane, Rockville, MD 20857.

(f) *Correction of patent information errors.* If any person disputes the accuracy or relevance of patent information submitted to the agency under this section and published by FDA in the list, or believes that an applicant has failed to submit required patent information, that person must first notify the agency in writing stating the grounds for disagreement. Such notification should be directed to the Office of Generic Drugs, OGD Document Room, Attention: Orange Book Staff, at the address identified on FDA's Web site 7500 Standish Pl., Rockville, MD 20855. The agency will then request of the applicable new drug application holder that the correctness of the patent information or omission of patent information be confirmed. Unless the application holder withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in the list. If the new drug application holder does not change the patent information submitted to FDA, a 505(b)(2) application or an abbreviated new drug application under section 505(j) of the act submitted for a drug that is claimed by a patent for which information has been submitted must, despite any disagreement as to the correctness of the patent information, contain an appropriate certification for each listed patent.

[59 FR 50363, Oct. 3, 1994; 68 FR 36703, June 18, 2003; 69 FR 13473, March 23, 2004; 74 FR 9766, March 6, 2009; 74 FR 36605, July 24, 2009]

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED UPON AND

NDA NUMBER

places of business within the United States)	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	☐ Yes	☐ No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	☐ Yes	☐ No

FORM FDA 3542 (12/08)

PSC Graphics (301) 443-1090

Department of Health and Human Services Food and Drug Administration	Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.
PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT ***For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation or Composition) and/or Method of Use***	NDA NUMBER NAME OF APPLICANT/NDA HOLDER

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME	
ACTIVE INGREDIENT(S)	STRENGTH(S)
DOSAGE FORM	APPROVAL DATE OF NDA OR SUPPLEMENT

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) within thirty (30) days after approval of an NDA or supplement or within thirty (30) days of issuance of a patent as required by 21 CFR 314.53(c)(2)(ii) at the address provided in 21 CFR 314.53(d)(4). To expedite review of this patent declaration form, you may submit an additional copy of this declaration form to the Center for Drug Evaluation and Research "Orange Book" staff.

For hand-written or typewriter versions of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
d. Name of Patent Owner	Address *(of Patent Owner)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

FORM FDA 3542 (12/08) Page 1

For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement?	☐ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA?	☐ Yes	☐ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.)	☐ Yes	☐ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug substance if:

- the answers to 2.1 and 2.2 are "No," or,
- the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,
- the answer to 2.3 is "Yes" and there is no response to 2.4, or,
- the answer to 2.5 or 2.6 is "Yes."
- the answer to 2.7 is "No."

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the approved drug product as defined in 21 CFR 314.3?	☐ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug product if:

- the answer to question 3.1 is "No," or,
- the answer to question 3.2 is "Yes," or,
- the answer to question 3.3 is "No."

4. Method of Use

Sponsors must submit the information in section 4 for each approved method of using the approved drug product claimed by the patent. For each approved method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more approved methods of using the approved drug product?		☐ Yes	☐ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in 4.1 claim an approved method of use of the approved drug product?	☐ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the approved labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*		

4.2b If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description.	Use: *(Submit the description of the approved indication or method of use that you propose FDA include on the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)*

FDA will not list the patent in the Orange Book as claiming the method of use if:

- the answer to question 4.1 or 4.2 is "No," or
- if the answer to 4.2 is "Yes" and the information requested in 4.2a and 4.2b is not provided in full.

5. Method of Payment

For this NDA or supplement, does one or more relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

☐ Yes

6. Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/ holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(3)(i) and (4)(i).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name	
Address	City/State
ZIP Code	Telephone Number
FAX Number *(if available)*	E-Mail Address *(if available)*

The public reporting burden for this collection of information has been estimated to average 3 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer (HFA-710)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542

PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.

- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.

- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use. Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."

- Only information from form 3542 will be used for Orange Book publication purposes.

- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.

- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.

- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the approved NDA or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be listed. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be listed as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the approved NDA or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims use or more methods of use of the drug product that is the subject of the approved NDA or supplement.

4.2) For each approved use of the drug claimed by the patent, identify by number the claim(s) in the patent that claim the approved use of the drug. An applicant may list together multiple patent claim numbers and information for each approved method of use, if applicable. However, each approved method of use must be separately listed within this section of the form.

4.2a) Specify the part of the approved drug labeling that is claimed by the patent.

4.2b) The answer to this question will be what FDA uses to create a "use-code" for Orange Book publication. The use code designates a method of use patent that claims the approved indication or use of a drug product. Each approved use claimed by the patent should be separately identified in this section and contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method of use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval. Use a maximum of 240 characters for each "use code."

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

OPPOSITION BRIEF

RECORD
AND
BRIEFS

FEB 25 2011

No. 10-844

IN THE

Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD. AND SUN PHARMACEUTICAL INDUSTRIES, LTD.,

Petitioners,

v.

NOVO NORDISK A/S AND NOVO NORDISK INC.,

Respondents.

On Petition For A Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

BRIEF IN OPPOSITION

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QUESTION PRESENTED

The Hatch-Waxman Act includes a narrow counterclaim under which, if a listed "patent does not claim ... an approved method of using the drug," a district court may order the patentee "to correct or delete the patent information submitted ... under subsection (b) or (c) of this section." 21 U.S.C. § 355(j)(5)(C)(ii). Petitioners concede that the patent here *does* claim an approved method of use, and they seek judicially ordered revision of information that was *not* submitted under the specified subsections of the statute and that is, in any event, correct. Thus, the "question presented" in the petition does not exist. Rather, the question presented is:

Whether the court of appeals correctly concluded, in a case of first impression, that neither the cause of action nor the remedy provided for by the Hatch-Waxman Act's counterclaim provision is available to petitioners on the particular facts of this case.

RULE 29.6 STATEMENT

Pursuant to this Court's Rule 29.6, undersigned counsel state that:

Novo Nordisk Inc. is a wholly owned subsidiary of Novo Nordisk US Holdings, Inc. No publicly held company owns 10% or more of Novo Nordisk Inc.'s stock. Novo Nordisk US Holdings, Inc. is a wholly owned subsidiary of Novo Nordisk A/S, a public limited liability company. Novo Nordisk A/S is the only publicly held company that owns 10% or more of Novo Nordisk US Holdings, Inc.'s stock.

Novo A/S, a private limited liability company, is Novo Nordisk A/S's controlling shareholder. No publicly held company owns 10% or more of Novo Nordisk A/S's stock. Novo A/S is a wholly owned subsidiary of the Novo Nordisk Foundation, a Danish self-governing institution. No publicly held company owns 10% or more of Novo A/S's stock.

Novo Nordisk Foundation has no parent company, and no publicly held company owns 10% or more of its stock.

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BRIEF IN OPPOSITION

Respondents Novo Nordisk A/S and Novo Nordisk Inc. respectfully submit that the petition for a writ of certiorari should be denied.

OPINIONS BELOW

The opinion of the court of appeals (Pet. App. 1a-52a) is reported at 601 F.3d 1359. The order denying rehearing (Pet. App. 53a-64a) is reported at 615 F.3d 1374. The district court's decisions on the counterclaim issue (Pet. App. 67a-72a & 73a-103a) are reported at 656 F. Supp. 2d 729 and 649 F. Supp. 2d 661. Its injunction (Pet. App. 65a-66a) is available at 2009 U.S. Dist. LEXIS 88551. Subsequent decisions of the district court on subject-matter jurisdiction (App., *infra*, 1a-10a) and validity and enforceability (App., *infra*, 11a-106a) are available at 2010 U.S. Dist. LEXIS 106729 and 2011 U.S. Dist. LEXIS 4889, respectively.

JURISDICTION

The court of appeals entered an interlocutory judgment on April 14, 2010, and denied rehearing on July 29, 2010. On October 18, 2010, the Chief Justice extended the time to file a petition for a writ of certiorari to and including December 23, 2010. No. 10A380. Petitioners invoke the jurisdiction of this Court under 28 U.S.C. § 1254(1).

The federal courts lack subject-matter jurisdiction over this dispute as a result of petitioners' election in April 2008 to withdraw their certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV"), on which jurisdiction previously rested (*see Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661, 678 (1990)), and to replace it with a statement under 21 U.S.C.

§ 355(j)(2)(A)(viii) ("section viii"), which does not support federal jurisdiction. *Compare Novo Nordisk Inc.* v. *Mylan Pharms. Inc.*, 2010 U.S. Dist. LEXIS 32569 (D.N.J. Mar. 31, 2010) (so holding), *with* App., *infra*, 1a-10a (contra). As explained below, this jurisdictional issue has not yet been reviewed by the Federal Circuit.

STATUTORY PROVISIONS INVOLVED

The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, commonly known as the Hatch-Waxman Act, amended various provisions of the Federal Food, Drug, and Cosmetic Act, including 21 U.S.C. § 355 (Pet. App. 104a-195a), and the Patent Act, including 35 U.S.C. § 271(e)(2) (App., *infra*, 108a-109a). The counterclaim provision at issue here (Pet. App. 145a-146a) states in full:

> **(ii) Counterclaim to infringement action**
>
> **(I) In general**
>
> If an owner of the patent or the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the [generic] applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) of this section on the ground that the patent does not claim either—
>
> (aa) the drug for which the application was approved; or

(bb) an approved method of using the drug.

(II) No independent cause of action

Subclause (I) does not authorize the assertion of a claim described in subclause (I) in any civil action or proceeding other than a counterclaim described in subclause (I).

21 U.S.C. § 355(j)(5)(C)(ii) (added by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066).

STATEMENT

The district court entered a "mandatory injunction" under the Hatch-Waxman Act's counterclaim provision, ordering respondents to alter the entirely correct "use code narrative" previously submitted to, and accepted by, the Food and Drug Administration in connection with a patented method of diabetes drug therapy. Pet. App. 65a-66a. The Federal Circuit—in the first appellate decision construing the Hatch-Waxman counterclaim since it was enacted by Congress in 2003—ruled that "[b]ecause [petitioners do] not have a statutory basis to assert a counterclaim requesting such injunctive relief, this court reverses and vacates the injunction." Pet. App. 2a-3a.

1. The Hatch-Waxman Act governs many aspects of the intense competition among makers of branded and generic drugs, including patented drug products and methods. *See generally Janssen Pharmaceutica, N.V.* v. *Apotex, Inc.*, 540 F.3d 1353, 1355-57 (Fed. Cir. 2008). In particular, Section 505 of the Federal Food, Drug, and Cosmetic Act, as amended by the Hatch-Waxman Act, regulates the process by which drug makers can secure FDA approval of new drugs, as well as the avenues of judicial relief avail-

able to patent holders and their generic competitors. *See* 21 U.S.C. § 355.

Section 505(a) prohibits the sale of a new drug "unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug." 21 U.S.C. § 355(a). Subsection (b) requires a pioneer company seeking to manufacture a new drug to file a new drug application (NDA), together with a variety of information on the safety and effectiveness of the drug. *See id.* § 355(b)(1)(A)-(G). Subsection (c) addresses amendments to and approval of NDAs, and authorizes certain lawsuits by the NDA holder to enforce its rights. *Id.* § 355(c)(1)-(3).

Section 505(b) requires the NDA applicant to "file ... the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug," and requires FDA to "publish information submitted under [that requirement]." 21 U.S.C. § 355(b)(1)(G). FDA publishes a list of patents claiming approved drug products or methods, along with the statutory "patent information" and other information required by regulation, in the "Orange Book." *See Janssen*, 540 F.3d at 1355.

Section 505(j) allows a generic competitor to file an abbreviated new drug application (ANDA) with FDA, relying on the research into safety and effectiveness previously conducted by a pioneer drug maker. It requires generic companies making ANDA filings to include a certification that (I) no patent covering the listed drug has been listed in the Orange Book; (II) the patent has expired; (III) the patent will expire on a particular date and approval of

the ANDA should be deferred until expiration; or (IV) the patent is invalid or will not be infringed by the manufacture, use, or sale of the generic drug. 21 U.S.C. § 355(j)(2)(A)(vii). If the applicant does not seek approval for a use that is patented, it may instead file a "section viii statement," and seek to "carve out" of its proposed label any patented uses. *Id.* § 355(j)(2)(A)(viii); *see Purepac Pharm. Co.* v. *TorPharm, Inc.*, 354 F.3d 877, 880 (D.C. Cir. 2004) ("whereas applicants use paragraph IV certifications to challenge the validity of admittedly applicable patents, they use section viii statements to assert that patents do not apply").

The Hatch-Waxman Act provides that the filing of a Paragraph IV certification by an ANDA applicant is an act of patent infringement. 35 U.S.C. § 271(e)(2)(A); *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S 661, 678 (1990). If the pioneer company brings suit within 45 days of receiving notice of the Paragraph IV certification, the FDA may not approve the ANDA for 30 months. 21 U.S.C. § 355(j)(5)(B)(iii). As an incentive for generic companies to bear the cost of such an infringement suit, the Hatch-Waxman Act grants the first company to submit a Paragraph IV certification for a particular drug a 180-day period of generic marketing exclusivity, during which time FDA will not approve a later-filed Paragraph IV ANDA based on the same NDA. *Id.* § 355(j)(5)(B)(iv).

In 2001, the Federal Circuit held that a generic competitor could not resist a Paragraph IV infringement suit on the ground that the asserted patent was improperly listed in the Orange Book. *Mylan Pharms., Inc.* v. *Thompson*, 268 F.3d 1323 (Fed. Cir. 2001). There, the ANDA applicant for generic BuSpar (buspirone hydrochloride) argued

that the patent listed in the Orange Book "did not claim BuSpar or an approved method of using BuSpar." *Id.* at 1331. The Federal Circuit held that the statute did not authorize judicial delisting of an improperly listed patent. *Id.* at 1332.

In 2003, the Hatch-Waxman Act was amended to respond to the *Mylan* decision by authorizing a limited counterclaim for ANDA filers in Paragraph IV lawsuits. The counterclaim (echoing the language of *Mylan*) requires the generic applicant to prove that the patent "does not claim ... the drug ... or ... an approved method of using the drug." 21 U.S.C. § 355(j)(5)(C)(ii)(I). If the generic applicant can carry this burden, it may "seek[] an order requiring the [patentee] to correct or delete the patent information submitted ... under subsection (b) or (c) of this section." *Ibid.*

Section 505(b) requires NDA filers to provide FDA with specified "patent information": "The applicant shall file with the application the *patent number* and the *expiration date* of any patent which claims the drug ... or which claims a method of using such drug." 21 U.S.C. § 355(b)(1)(G) (emphases added). Section 505(c) states that "[i]f the patent information described in subsection (b) of this section could not be filed with the submission of an application," the holder of an approved application "shall file with the Secretary the *patent number* and the *expiration date* of any patent which claims the drug ... or which claims a method of using such drug." *Id.* § 355(c)(2) (emphases added).

Separate and apart from the "patent information" specifically required of NDA filers by subsections (b) and (c) (*i.e.*, the patent number and expiration date), FDA has promulgated regulations that

require NDA applicants to provide additional information not mandated by statute. *See* 68 Fed. Reg. 36,676, 36,703-05 (June 18, 2003) (codified at 21 C.F.R. pt. 314) (Pet. App. 196a-210a); 72 Fed. Reg. 21,266, 21,268-69 (Apr. 30, 2007). This information is provided to FDA on Form 3542 (Pet. App. 211a-214a), and includes "the description of the approved indication or method of use" for a drug. Pet. App. 213a; *see also* 21 C.F.R. § 314.53(c)(2)(ii)(P). This description (provided in Box 4.2b of the form) is popularly known as the "use code narrative." FDA includes use code narratives with the statutory "patent information" in the Orange Book.

2. Respondents sell the drug repaglinide under the brand name PRANDIN®. Repaglinide is approved for treating diabetes when used alone (monotherapy) or in combination with other specified drugs. C.A. App. A464; A821-A839. In 2004, respondents were issued U.S. Patent No. 6,677,358, Claim 4 of which claims a method for using repaglinide in combination with metformin to treat type 2 diabetes. C.A. App. A69-A79. Following the issuance of the '358 patent, respondents submitted a proposed use code narrative to FDA (C.A. App. A801-A803), which published the following use code in the Orange Book: "U-546—Use of repaglinide in combination with metformin to lower blood glucose." C.A. App. A888; A1234-A1235.

In 2005, petitioners filed an ANDA for generic repaglinide that included a Paragraph IV certification that the '358 patent was invalid or would not be infringed by the sale of generic repaglinide. C.A. App. A239-A242. Respondents sued for infringement under the provisions of the Hatch-Waxman Act. Petitioners eventually stipulated that its ANDA for repaglinide would infringe the '358 patent if it "in-

clude[d] a label that discusses the combination of metformin and repaglinide." C.A. App. A236; *see also* Pet. 19 n.10.

In April 2008, petitioners amended their ANDA and, with respect to Claim 4, replaced their Paragraph IV certification with a section viii statement that would "carve out" repaglinide-metformin combination therapy from its otherwise infringing label. C.A. App. A257-A260. In December 2008, the FDA indicated that this carve-out would be permitted. C.A. App. A625-A643. Shortly thereafter, respondents moved for reconsideration on the ground that allowing this carve-out would render generic repaglinide less safe and effective. C.A. App. A644-A657; *see also* C.A. App. A658-A663.

During the same time period, respondents revised the PRANDIN® label pursuant to an FDA directive "requesting changes to the professional labeling of all oral anti-diabetic drugs." C.A. App. A667. This FDA directive required respondents to "[r]eplace all the separate indications (e.g., monotherapy, combination therapy, and initial or second-line therapy) with the following sentence: 'Prandin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.'" C.A. App. A667-A668.

In May 2009, respondents submitted an amended FDA Form 3542, which included an updated use code narrative to reflect precisely the new FDA-mandated indication for PRANDIN®. C.A. App. A670-A674. Respondents explained to FDA that "[t]he information being submitted is to amend the use code relating to [the '358 patent] to correspond with the change in labeling required by FDA in [its directive]." C.A. App. A670. FDA published the following use code in

the Orange Book: "U-968—A method for improving glycemic control in adults with type 2 diabetes mellitus." C.A. App. A912; A840.

FDA then determined that respondents' request for reconsideration was "moot" in light of the new use code, as the "factual predicate" on which FDA's permissive carve-out decision had rested no longer applied. C.A. App. A664-A666. Despite repeated entreaties from petitioners, FDA declined to allow their section viii carve-out. C.A. App. A810-A814; A815-A820. Petitioners are thus required to include repaglinide-metformin combination therapy in their labeling, which is stipulated to infringe Claim 4 of the '358 patent, the only claim at issue in this case. C.A. App. A236-A238.

3. After FDA declined to allow petitioners to proceed under section viii, they sought in the district court "an order requiring [respondents] to correct the use code information submitted by [respondents]." C.A. App. A1259. As a statutory basis, they cited the counterclaim added by the 2003 amendments to the Hatch-Waxman Act. *Ibid.* Respondents resisted on the ground that both the cause of action asserted and the relief sought were not authorized by that counterclaim provision.

The district court denied respondents' motion to dismiss the "use code" counterclaim (Pet. App. 73a-103a) and later granted summary judgment to petitioners on this counterclaim (Pet. App. 67a-72a). The district court directed respondents by "mandatory injunction" to "submit[] to FDA an amended Form FDA 3542 that reinstates its former U-546 listing for Prandin and describes claim 4 of the '358 patent in section 4.2b as covering 'the use of repaglinide

in combination with metformin to lower blood glucose.'" Pet. App. 65a-66a.

4. On respondents' interlocutory appeal, the Federal Circuit vacated the injunction in the 2-1 decision that is the subject of this petition. Pet. App. 1a-52a.

The majority, "detect[ing] no ambiguity in the statutory language," held that "the Hatch-Waxman Act authorizes a counterclaim only if the listed patent does not claim any approved methods of using the listed drug." Pet. App. 12a. This result, the majority explained, was compelled by the text, structure, and history of the counterclaim provision, including the Federal Circuit's *Mylan* decision. Pet. App. 11a-14a. Because petitioners conceded that the listed patent "*does* claim an approved method of use" (C.A. Stay Opp. 13), the counterclaim was not available to petitioners.

The majority also held that "the terms of the counterclaim provision do not authorize an order compelling the patent holder to change its use code narrative." Pet. App. 14a-15a. That is because the counterclaim provision only authorizes an order compelling the patentee "to correct or delete *the patent information* submitted ... under subsection (b) or (c)" (21 U.S.C. § 355(j)(5)(C)(ii)(I) (emphasis added)), and "the Act defined the term 'patent information' as 'the patent number and the expiration date.'" Pet. App. 15a (citing *Valley Drug Co.* v. *Geneva Pharms. Inc.*, 344 F.3d 1294, 1296-97 (11th Cir. 2003)). Thus the counterclaim, even if available, did not authorize the injunction that the district court issued.

Concurring, Judge Clevenger "agree[d] with Judge Rader's analysis of the relevant statutory provisions in this case and therefore join[ed] the opinion

he writes for the court." Pet. App. 19a. Judge Clevenger wrote separately to emphasize that "Novo did nothing that was illegal or forbidden" and that "there is nothing illegal, or even incorrect, about Novo's current use code." Pet. App. 19a, 21a.

Judge Dyk dissented, urging adoption of petitioners' expansive reading of the counterclaim provision and arguing that "[a]n error in an Orange Book use code" should be "subject to correction" under the counterclaim provision. Pet. App. 43a; *see also* Pet. App. 57a-64a (Gajarsa, J., dissenting from denial of rehearing).

5. Following the Federal Circuit's interlocutory decision, proceedings on the remaining issues resumed in the district court.

Respondents renewed their motion to dismiss the lawsuit for lack of subject-matter jurisdiction, arguing that petitioners' decision to convert from a Paragraph IV certification to a section viii statement defeated the jurisdictional basis for suit. The district court, however, denied that motion. App., *infra*, 1a-10a.

On January 19, 2011, after a bench trial, the district court issued a decision concluding that Claim 4 is both invalid for obviousness and unenforceable for inequitable conduct. App., *infra*, 11a-106a. Respondents have filed a notice of appeal from the judgment entered contemporaneously with that decision.

REASONS FOR DENYING THE PETITION

The decision below is correct and does not conflict with any decision of this Court or any court of appeals. Moreover, the interlocutory nature of the decision and an antecedent jurisdictional problem make this case an inappropriate one in which to re-

solve the scope of the Hatch-Waxman Act's counterclaim provision.

I. THIS IS AN INAPPROPRIATE VEHICLE IN WHICH TO REVIEW THE SCOPE OF THE HATCH-WAXMAN COUNTERCLAIM

This is the first case in which any court has substantively construed or applied the Hatch-Waxman Act's counterclaim in a published or electronically available decision. Although petitioners assert that the issue is "recurring" (Pet. 17), they cannot identify any other case in which it has arisen in the past, and there is nothing to suggest that it will arise again any time soon. That is reason enough to deny the petition. *Boag* v. *MacDougall*, 454 U.S. 364, 368 (1982) (Rehnquist, J., dissenting) ("'To remain effective, the Supreme Court must continue to decide only those cases which present questions whose resolution will have immediate importance far beyond the particular facts and parties involved'") (quoting Chief Justice Vinson, Address before the American Bar Association (Sept. 7, 1949)).

Although petitioners and their *amici* suggest that the decision below has implications for the entire generic pharmaceutical industry, it is actually limited to the narrow, and perhaps unique, circumstances of this case, where a method (not product) claim recites some (but not all) FDA-approved uses of a drug, FDA has mandated a broad approved indication for the drug that includes both patented and non-patented uses, and the brand manufacturer has submitted a use code for its patented method that precisely tracks the FDA-mandated indication.

The leading generic companies and their trade association have all filed briefs in this Court, but they have not identified a single other patent listed in the Orange Book with these characteristics. On

the contrary, they ask the Court to "assume" that hypothetical (and unlikely) scenarios might be affected by the decision below. *See* Apotex Br. 4 ("assume" a scenario involving "drug X"); Mylan Br. 9 ("assume" a scenario involving "disease 1" and "disease 2").

Petitioners' bid to make the issue sound more important than it is rests on their hyperbolic assertion that the Federal Circuit's construction of the counterclaim, which is available only in Paragraph IV infringement proceedings, somehow "eviscerates" the section viii procedure, which is an *alternative* to Paragraph IV. Pet. 19. This is every bit the *non sequitur* it appears to be. Section viii and Paragraph IV are mutually exclusive—the ANDA applicant must choose one or the other. *Purepac Pharm. Co.* v. *TorPharm, Inc.*, 354 F.3d 877, 882 (D.C. Cir. 2004). If the generic proceeds via section viii, the counterclaim is *never* available under *any* circumstances: By its terms, the counterclaim applies *only* in infringement suits brought in response to a Paragraph IV certification. 21 U.S.C. § 355(j)(5)(C)(ii). The counterclaim was enacted in response to *Mylan*, a Paragraph IV case, and section viii was not even on the congressional radar screen. Indeed, the counterclaim has *nothing to do* with section viii carve-outs, rendering many of the arguments advanced by petitioners and their *amici* entirely irrelevant.

The counterclaim issue arose in this case only because petitioners first submitted a Paragraph IV certification, provoking an infringement suit by respondents; then, *after stipulating to infringement*, converted to a section viii statement that sought to carve out the patented methods of use; and then proceeded to assert the counterclaim in the (Paragraph IV) infringement litigation. To the extent the deci-

sion below precludes such an applicant from invoking the counterclaim, it simply ensures a level playing field with generics who attempt to avoid litigation by proceeding under section viii.

Moreover, the unusual arc of this litigation gives rise to two case-specific issues that are independent impediments to immediate review of the counterclaim issue: Caraco's conversion from Paragraph IV to section viii deprived the federal courts of jurisdiction, and the district court's ensuing judgment (if not *ultra vires*) could effectively moot the issue relating to the counterclaim.

A. The Federal Courts Lack Jurisdiction Over The Dispute

This Court must satisfy itself of its jurisdiction at the threshold before proceeding to the merits. *Steel Co.* v. *Citizens for a Better Env't*, 523 U.S. 83, 88-89 (1998); *Permoli* v. *New Orleans*, 44 U.S. (3 How.) 589, 609 (1845). Accordingly, certiorari will be denied in the absence of federal jurisdiction. *Good Shot* v. *United States*, 179 U.S. 87, 88-89 (1900) ("the writ of certiorari cannot properly be issued to require the court to send up a cause over which it has no jurisdiction for determination on the merits"); *see also*, *e.g.*, *California* v. *Gordon*, 420 U.S. 938 (1975) ("Certiorari denied, there being no present case or controversy such as to confer jurisdiction on this Court"); *Lawrence* v. *Arizona*, 269 U.S. 585 (1926) (per curiam).

In this case, respondents raised a substantial jurisdictional challenge in the district court—*viz.*, that petitioners deprived the federal courts of subject matter jurisdiction over the case when they converted from a Paragraph IV certification to a section viii statement as to Claim 4 of the '358 patent. This

jurisdictional issue was decided by the district court only after the Federal Circuit issued the decision that petitioners ask this Court to review. *See* App., *infra*, 1a-10a. As a result, the jurisdictional issue has not yet been reviewed by the Federal Circuit.

The Hatch-Waxman Act provides for jurisdiction in ANDA cases if and only if the generic applicant maintains a Paragraph IV certification with regard to the patent claim(s) at issue. *See Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661, 678 (1990) (Section 271(e)(2) of the Patent Act, 35 U.S.C. § 271(e)(2), creates "a highly artificial act of infringement that consists of submitting an ANDA ... containing *the fourth type of certification* that is in error as to whether commercial manufacture, use, or sale of the new drug (none of which, of course, has actually occurred) violates the relevant patent") (emphasis added). If the generic applicant's ANDA does not contain an effective Paragraph IV certification with respect to the patent claim-in-suit, there is no federal jurisdiction.

Although petitioners originally filed a Paragraph IV certification with respect to Claim 4 of the '358 patent, initially creating jurisdiction for this lawsuit, they subsequently amended their ANDA by withdrawing the Paragraph IV certification and replacing it with a section viii statement. *See* 21 C.F.R. § 314.94(a)(12)(viii) ("Once an amendment ... is submitted, the [ANDA] application will no longer be considered to contain the prior certification").

The Hatch-Waxman Act does not provide for jurisdiction where an ANDA applicant files a section viii statement. *See Purepac Pharm. Co.* v. *Thompson*, 238 F. Supp. 2d 191, 195 (D.D.C. 2002), *aff'd*, 354 F.3d 877 (D.C. Cir. 2004). The Declaratory

Judgment Act includes express statutory limitations on declaratory judgment actions in the patent context (*see* 28 U.S.C. § 2201(b); 35 U.S.C. § 271(e)(5)) and, in any event, "is not an independent source of federal jurisdiction." *Schilling* v. *Rogers*, 363 U.S. 666, 677 (1960). Thus, there is no basis for federal jurisdiction in a lawsuit involving a patent claim subject only to a section viii statement, as this one is.

Elementary principles of federal jurisdiction require that a justiciable controversy exist not only at the initiation of a lawsuit but throughout. *Arizonans for Official English* v. *Arizona*, 520 U.S. 43, 67 (1997). Thus, petitioners' strategic choice to proceed under section viii rather than Paragraph IV divested the federal courts of jurisdiction over any challenges involving Claim 4 of the '358 patent—the only patent claim at issue in this litigation.

Another district court considering a different manufacturer's ANDA for the same drug (generic repaglinide) has squarely held that the absence of a Paragraph IV certification as to Claim 4 of the '358 patent means that there is no federal jurisdiction. *Novo Nordisk Inc.* v. *Mylan Pharms. Inc.*, 2010 U.S. Dist. LEXIS 32569, at *26-31 (D.N.J. Mar. 31, 2010). To be sure, the district court in this case reached the directly contrary conclusion (App., *infra*, 1a-10a); but that conflict will be presented to the Federal Circuit for resolution on appeal from the final judgment in this case. That appeal, however, has yet to be briefed, argued, or decided.

Thus, if the Court were to grant certiorari to review the scope of the Hatch-Waxman counterclaim, it would first have to resolve the jurisdictional issue without benefit of the court of appeals' analysis. *See DTD Enters.* v. *Wells*, 130 S. Ct. 7, 8 (2009) (state-

ment of Kennedy, J., respecting denial) ("If [the Court] were to grant the petition [it] would be required to ... confront a procedural obstacle unrelated to the question presented"); *see also, e.g.*, *Wrotten* v. *New York*, 130 S. Ct. 2520, 2520 (2010) (statement of Sotomayor, J., respecting denial) ("Granting the petition for certiorari at this time would require [the Court] to resolve the threshold [jurisdictional] question"). "Under these circumstances, it is best to deny the petition." *DTD*, 130 S. Ct. at 8 (statement of Kennedy, J.).

B. The Counterclaim Issue Would Be Reviewable After Final Decision

Furthermore, following the decision of the Federal Circuit challenged in the petition, the district court proceeded to resolve petitioners' challenges to the validity and enforceability of Claim 4 of the '358 patent. Those issues too remain to be decided by the Federal Circuit.

Where "[t]he decree that was sought to be reviewed by certiorari ... was not a final one, [that] fact ... alone furnishe[s] sufficient ground for the denial of the application." *Hamilton-Brown Shoe Co.* v. *Wolf Bros. & Co.*, 240 U.S. 251, 258 (1916). This is because "a mere denial of the writ to an interlocutory ruling of the Circuit Court of Appeals does not limit [the Court's] power to review the whole case when it is brought here by ... certiorari on final decree." *Toledo Scale Co.* v. *Computing Scale Co.*, 261 U.S. 399, 418 (1923); *see also Hamilton-Brown Shoe*, 240 U.S. at 258.

Thus, if the Court declines interlocutory review and waits for a petition for certiorari from a final judgment, it is able to evaluate all of the issues, presented together on a fully developed record, with no

attendant prejudice to any party. This approach also alleviates the risk that the issue will become moot or otherwise of diminished significance in light of the final disposition. *Am. Constr. Co.* v. *Jacksonville, Tampa & Key West Ry. Co.*, 148 U.S. 372, 384 (1893) ("many orders made in the progress of a suit become quite unimportant by reason of the final result, or of intervening matters"). Therefore, as a matter of course, and regardless of the importance of the legal issues presented, this Court traditionally declines review of interlocutory decisions. *Va. Military Inst.* v. *United States*, 508 U.S. 946 (1993) (Op. of Scalia, J., respecting denial) ("We generally await final judgment in the lower courts before exercising our certiorari jurisdiction").

Petitioners seek review of an interlocutory injunction, from which respondents took an interlocutory appeal to the Federal Circuit. Subsequent to the filing of the petition for a writ of certiorari, the district court decided petitioners' invalidity and unenforceability counterclaims. Respondents have noticed an appeal to the Federal Circuit. Rather than reviewing this case piecemeal, the better course is for this Court to decline certiorari now. It can then review, if necessary, any issues that the parties may wish to bring to its attention, in a single proceeding, after the Federal Circuit decides the remaining issues in this case.

Moreover, if either the invalidity or unenforceability holding were affirmed (assuming, *dubitante*, the existence of federal jurisdiction), the counterclaim issue could be rendered of little or no continuing importance to petitioners. It makes little sense for this Court to invest its resources, or the parties theirs, on an issue that might be rendered inconsequential by the pending appeal.

II. THE FEDERAL CIRCUIT CORRECTLY CONSTRUED THE SCOPE OF THE HATCH-WAXMAN COUNTERCLAIM

Although petitioners complain that the Federal Circuit "violated numerous precedents of this Court, including precedent interpreting the Hatch-Waxman Act itself" (Pet. 17), they concede that this Court "has never addressed the Act's provisions governing approval of generic marketing" (*id.* at 5). The claimed conflict with this Court's decisions—like their prediction of impending "disaster" (*id.* at 35)—is, to put it mildly, wildly overstated.

The counterclaim provision states that, if the generic company defendant in a Paragraph IV lawsuit proves that "the patent does not claim ... an approved method of using the drug," the court may order the patentee "to correct or delete the patent information submitted ... under subsection (b) or (c) of this section." 21 U.S.C. § 355(j)(5)(C)(ii). The Federal Circuit construed this provision by applying well-settled principles of statutory construction. *See, e.g.*, *Hughes Aircraft Co.* v. *Jacobson*, 525 U.S. 432, 438 (1999) ("statutory construction ... begins with the language of the statute") (internal quotation marks omitted); *Barnhart* v. *Thomas*, 540 U.S. 20, 26 (2003) (construction favored that is "quite sensible as a matter of grammar"); *Envtl. Def.* v. *Duke Energy Corp.*, 549 U.S. 561, 574 (2007) (identical words used in the same act are presumed to have the same meaning).

Using these unchallenged tools, the court of appeals held that the text and structure of the Hatch-Waxman Act establish that the counterclaim is not available if the patent-in-suit *does* claim "an approved method of using the drug," even if other ap-

proved methods are not patented; and that the "patent information" subject to correction or deletion is limited to the patent number and expiration date—the only "information" required by (or even mentioned in) Section 505(b) and (c). Pet. App. 11a-16a.

Petitioners acknowledge, as they must, that the construction of the counterclaim provision adopted by the majority below is consistent with the statutory language. Pet. 30 (conceding "that 'an,' when qualified by a negative, *can* mean 'any'") & 35 (conceding that "§ 505(b) and (c) mention only the patent number and expiry"). That should end the matter, since the Judiciary's "charge is to give effect to the law Congress enacted." *Lewis* v. *City of Chicago*, 130 S. Ct. 2191, 2200 (2010). *All* of the policy arguments advanced by petitioners and their *amici* suggest, at most, "a problem for Congress, not one that federal courts can fix." *Ibid.*

A. The Counterclaim Is Not Available Where The Patent Claims An Approved Method Of Use

The majority in the court below explained that the counterclaim was enacted to "correct the specific issue raised in *Mylan*, *i.e.*, to deter pioneering manufacturers from listing patents that were not related at all to the patented product or method" (Pet. App. 13a), and it is undisputed that the construction of the counterclaim adopted in this case entirely addresses the *Mylan* situation.

In *Mylan*, the Federal Circuit held that a generic competitor could not obtain judicial relief to delist an improperly listed patent because it "did not claim ... an approved method of using [the drug]." 268 F.3d 1323, 1331 (Fed. Cir. 2001). Because a delisting cause of action was not explicitly authorized by the Hatch-Waxman Act, the court reasoned that Mylan's

suit was "an impermissible attempt by a private party to enforce the [Federal Food, Drug, and Cosmetic Act]." *Id.* at 1329-30 (citing *Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341 (2001)). In response, Congress enacted a narrow provision authorizing a counterclaim to delete or correct patent information where "the patent does not claim .... an approved method of using the drug." 21 U.S.C. § 355(j)(5)(C)(ii)(I)(bb). The majority's construction ensures that the counterclaim is available in the *Mylan* situation, and thus fully effectuates the 2003 amendment. Petitioners' argument that the majority unduly limited the counterclaim is nothing other than a policy-based plea to extend it *beyond* the *Mylan* situation that Congress set out to address. *See* Pet. App. 21a (Clevenger, J., concurring) ("The counterclaim statute, which the dissent would expand beyond its literal reach, was designed to cure the situation presented in *Mylan*.").

Under the counterclaim, *if* a patent was improperly listed because it does not claim an approved method of using the drug, *then* the court may order the deletion or correction of the "patent information." In this case, however, petitioners have conceded that respondents' '358 patent "is properly listed in the Orange Book" because it "covers an FDA-approved method of using the referenced drug." C.A. App. A675; *see also* C.A. Stay Opp. 13 (petitioners' concession that the '358 patent "*does* claim an approved method of use"). There is thus nothing to delete or correct.

The operative language of the counterclaim provision requires the generic competitor to prove that the listed patent "does not claim ... an approved method" of using the drug. In light of their concession, petitioners argue that "an approved method" should be interpreted as "all approved methods" or "every approved method." As the majority explained,

however, "[w]hen an indefinite article is preceded and qualified by a negative, standard grammar generally provides that 'a' means 'any.'" Pet. App. 12a (citing dictionary definitions). Indeed, that is the *only* definition dictionaries provide where, as here, the article is preceded and qualified by a negative ("does not claim"). *See* Random House Webster's Unabridged Dictionary 1 (2d ed. 2001) (defining the indefinite article "a" as "any" in the example "not a one"); American Heritage Dictionary of the English Language 1 (4th ed. 2006) (defining "a" solely as "[a]ny" in the example "not a drop to drink").

Petitioners further concede that "'an,' when qualified by a negative, *can* mean 'any.'" Pet. 30. That concession is fatal: The majority made an interpretative decision, applying a clearly accepted definition of the word "an." It did not "rewr[i]te the statute" or "change[] the statute's meaning," in contravention of the principles of statutory interpretation, as petitioners allege. Pet. 30-31.

Petitioners' objection that "an approved method" does not *necessarily* mean "any approved method" (*see* Pet. 30-31) is unsupported by any authority and irreconcilable with the doctrine that statutes are to be read *in pari materia*. The Hatch-Waxman Act requires listing of patents that claim "*a* method of using such drug" (21 U.S.C. § 355(b)(1)) and the counterclaim is available if the owner of a patent "for the drug ... *a* use of which is claimed by the patent" initiates an infringement action (*id.* § 355(j)(5)(C)(ii)(I)) (both emphases added). In both instances it is clear from context that the indefinite article "a" means *any*, as petitioners have previously acknowledged. Pet. C.A. Br. 38 n.2 ("an NDA holder may list a patent if it covers any approved use"). Reading "an approved method" the same way is the only way to harmonize the statute as a whole, as the majority correctly recognized. Pet. App. 12a ("Therefore, the

Hatch-Waxman Act authorizes a counterclaim only if the listed patent does not claim any approved methods of using the listed drug").

The dissenting judge below acknowledged that adopting petitioners' alternative construction would require reading into the statute a word—"associated"—that Congress did not include. *See* Pet. App. 42a-43a (suggesting that the counterclaim provision be judicially amended to read "does not claim ... an [associated] approved method"). But adding a term to a statute "from which it is conspicuously absent more closely resembles inventing a statute rather than interpreting one." *Hardt* v. *Reliance Standard Life Ins. Co.*, 130 S. Ct. 2149, 2156 (2010) (internal quotation marks omitted).

Petitioners contend, however, that the majority "'render[ed] superfluous' the term 'correct.'" Pet. 32 (citing *Astoria Fed. Sav. & Loan Ass'n* v. *Solimino*, 501 U.S. 104, 112 (1991)). Not so: If a patent was improperly listed because it does not claim an approved method of using the drug, then the court may order either delisting or correction of the patent number and expiration date. In most cases in which a generic competitor proves that the listed patent does not claim an approved method, the appropriate remedy will be delisting. *See* 21 U.S.C. § 355(b)(1) (listing requirement applies to "any patent ... which claims a method of using such drug"). But there may also be instances in which the NDA holder lists the wrong patent: A brand-name company with a large portfolio of patents, with several patents in similar fields of use, could well have multiple NDA applications on related drugs and methods. If an error were made in listing a patent (for example, the wrong patent number were given), the Hatch-Waxman counterclaim authorizes the court to order correction of the listed patent number without requiring a resubmission by the NDA holder. In this way, Congress

completely addressed the *Mylan* situation that prompted the 2003 amendment.

There is good reason to restrict the counterclaim to the *Mylan* situation under this Court's precedents. The counterclaim is an *exception* to the rule that private litigants may not challenge submissions to FDA (*Buckman*, 531 U.S. at 348-51), and must be construed narrowly to avoid swallowing that rule. (Tellingly, petitioners do not cite *Buckman* or attempt to address this point.) If the counterclaim is to be extended beyond *Mylan*, then such an extension is a task for Congress, not this Court. *See Microsoft Corp.* v. *AT&T Corp.*, 550 U.S. 437, 457 (2007) (any such "'loophole' ... is properly left for Congress to consider, and to close if it finds such action warranted"); *Cardiac Pacemakers, Inc.* v. *St. Jude Med., Inc.*, 576 F.3d 1348, 1362-65 (Fed. Cir. 2009) (en banc) ("it is Congress's right, not the courts', to extend the statute beyond the ... problem it was designed to fix").

Contrary to petitioners' contention (Pet. 1, 27-29), the decision below is not "inconsistent" or in "conflict" with *Teva Pharm. USA, Inc.* v. *Sebelius*, 595 F.3d 1303 (D.C. Cir. 2010). The D.C. Circuit did not construe the Hatch-Waxman counterclaim; rather, it referenced the provision in passing in construing an entirely different provision of the Hatch-Waxman Act, in a manner that is entirely consistent with the Federal Circuit's reading of the counterclaim provision. *See id.* at 1315 n.4 ("The purpose of this [counterclaim] procedure, says Teva, is to offer generics a means of combating brand companies' practice of delaying generic competition by listing 'sham patents,' baiting a generic into filing a paragraph IV certification, and then filing an infringement suit").

Moreover, both *Teva* and the decision below make clear that it is *Congress's* role to balance the interests of brand and generic manufacturers, and that FDA and the courts must respect and adhere to such congressional determinations (including the compromises they inevitably reflect). *Compare Teva*, 595 F.3d at 1316 ("FDA may not ... change the incentive structure adopted by the Congress," for "the agency is bound not only by the ultimate purposes Congress has selected but by the means it has deemed appropriate") (emphasis and internal quotation marks omitted), *with* Pet. App. 16a (agency interpretations that are "at odds with the plain language of the statute itself" serve to "upset the careful balance" of the statute and must be rejected). Both courts are in full agreement that the statute must be enforced as written. That is of course this Court's view too. *Lewis*, 130 S. Ct. at 2200.

The supposed "inconsistent[cy]" is simply that the D.C. Circuit interpreted the statutory language at issue in *Teva* in the manner urged by the generic manufacturer, while the Federal Circuit interpreted the entirely different language of the counterclaim provision in the manner proposed by the branded company. This is not the kind of "obvious conflict with any other Circuit" that would constitute "special circumstances that justify the exercise of our discretionary certiorari jurisdiction to review the Court of Appeals' [review] of the interlocutory order entered by the District Court." *Office of Senator Dayton* v. *Hanson*, 550 U.S. 511, 515 (2007). Rather, it simply reflects that the Hatch-Waxman Act, like most complex federal legislation, does not uniformly benefit any particular constituency, but instead strikes a balance between competing interests—here, branded and generic competitors. Petitioners and their *amici*

obviously would prefer that the balance be tipped toward the generic industry, but that is a policy argument appropriately addressed only to Congress, not this Court.

B. The Remedy Is Limited To Correction Or Deletion of Patent Numbers And Expiration Dates

Even if the counterclaim were available to petitioners, the relief they seek—a judicial order requiring respondents to withdraw the current use code narrative and replace it with one approved by petitioners—is not authorized by the Hatch-Waxman Act.

The only relief authorized by the Hatch-Waxman counterclaim is an order requiring the NDA holder "to correct or delete the patent information submitted by the holder under subsection (b) or (c)." 21 U.S.C. § 355(j)(5)(C)(ii)(I). The incorporated provisions require the submission (and publication) of very specific "patent information"—the "patent number" and its "expiration date." *Id.* § 355(b), (c). As the majority recognized, "the Act defined the term 'patent information' as 'the patent number and the expiration date,'" and "to maintain consistency in the statutory terms, 'the patent information' in the counterclaim provision must also mean the patent number and the expiration date." Pet. App. 15a.

Importantly, petitioners do not dispute that the Federal Circuit's construction *of the statute* is permissible. On the contrary, they recognize that "§ 505(b) and (c) mention *only* the patent number and expiry." Pet. 35 (emphasis added). Accordingly, they do not take issue with the majority's statutory exegesis, which is entirely consistent with the legislative history of the counterclaim provision as well as

its underlying purpose (*i.e.*, allowing challenges to improperly listed patents).

Rather, petitioners maintain that FDA has by regulation interpreted the term "patent information" to include use code narratives in addition to the patent number and expiration date, and that this interpretation is entitled to deference. Pet. 34-35. Indeed, petitioners go so far as to say that certiorari is warranted because the majority's ruling that statutory "patent information" is limited to the patent number and expiration date, and not use codes—which are nowhere mentioned in the statute—"violates *Chevron [U.S.A. Inc.] v. NRDC, Inc.*, 46[7] U.S. 8[3]7 (1984)." Pet. 34.

Petitioners' "deference" argument rests on the premise that FDA promulgated a regulation in 2003 "defini[ng]" "patent information" to include "use code narratives," and that Congress acted "with full awareness of the agency's interpretation," effectively "adopt[ing]" and "implement[ing]" this "definition." Pet. 34. That premise, however, is false.

The FDA regulation on which petitioners rely is entitled "[s]ubmission of patent information" and requires the submission of certain information, including use code narratives. *See* 21 C.F.R. § 314.53; 68 Fed. Reg. 36,676, 36,703-05 (June 18, 2003). But petitioners fail to inform the Court of the rest of the story. In 2006, an industry group challenged FDA's regulatory authority to require use code narratives. In response, FDA did *not* justify this requirement as an interpretation of "patent information" in subsection (b) or (c); rather, FDA said—in a formal statement not cited by petitioners or any of their *amici*—that it was authorized to require use code narratives under its general rulemaking authority and subsection (j). 72 Fed. Reg. 21,266, 21,268-69 (Apr. 30, 2007) (describing submission of use codes as a "regu-

latory requirement"). In other words, FDA acknowledged that use code narratives are *not* "patent information" under Section 505(b) or (c), and it does not purport to have offered the "interpretation" that petitioners posit. Courts need not defer to an interpretation that the agency itself denies making.

Moreover, even if (counterfactually) FDA *had* interpreted "patent information" to include use code narratives, "'no deference is due to agency interpretations at odds with the plain language of the statute itself.'" Pet. App. 16a (quoting *Pub. Emps. Ret. Sys.* v. *Betts*, 492 U.S. 158, 171 (1989)). The statute, by defining "patent information" as including just two things, precludes any regulatory effort to include a third thing. And nothing in the counterclaim provision purports to alter that preexisting statutory definition. On the contrary, the counterclaim provision repeats that it is "the patent information submitted by the holder under subsection (b) or (c)" that may be corrected or deleted. 21 U.S.C. § 355(j)(5)(C)(ii)(I).

Where, as here, the statutory text and structure unambiguously limit "patent information" to the patent number and expiration date, there is no "gap" for the agency to fill. *Chevron*, 467 U.S. at 843. But even if Congress had been silent on this issue, FDA is not "entrusted to administer" a statutory provision establishing a judicial counterclaim for private plaintiffs—and thus FDA's purported interpretation of the terms of this statutory provision is of no help to petitioners. *Id.* at 844. It "is most certainly incorrect to say that language in a regulation can conjure up a private cause of action that has not been authorized by Congress. Agencies may play the sorcerer's apprentice but not the sorcerer himself." *Alexander* v. *Sandoval*, 532 U.S. 275, 291 (2001).

Congress specifically required two pieces of "patent information," and provided a counterclaim to cor-

rect or delete that information; had Congress wanted instead for the counterclaim to reach any other information that might be required by FDA (now or in the future), it would not have tied the counterclaim so specifically to the "patent information" submitted "under subsections (b) or (c)." *See, e.g., Blue Chip Stamps* v. *Manor Drug Stores*, 421 U.S. 723, 734 (1975) ("When Congress wished to provide a remedy ... , it had little trouble in doing so expressly"). Moreover, reading the statute as broadly as petitioners propose would render the express limitation superfluous, in contravention of another canon of construction. *TRW Inc.* v. *Andrews*, 534 U.S. 19, 31 (2001).

Petitioners rather breathlessly maintain that the decision below "expressly invalidates" the FDA's regulations requiring NDA holders to submit a broad range of information beyond the minimum required by the statute, including use codes. Pet. i, 23-27. According to petitioners, the decision therefore "throws a wrench in the FDA's ability to enforce provisions essential to the [Act's] operation." Pet. 23-24 (internal quotation marks omitted).

In truth, the majority decision does not invalidate any regulation, nor does it call into question FDA's authority to require the submission of use codes (or any other data) under its general rulemaking authority. And it does not in any way impact or undermine FDA's ability to enforce the Act's patent listing provisions. The same FDA regulations that were implemented and enforced before the decision continue to be implemented and enforced now. The same Form 3542 that was used by FDA to collect information from NDA holders then is used now, and must be completed by each NDA holder. It is simply not accurate to claim, as petitioners do, that the majority ruling "deprives the agency of information it 'must have' to expedite [its] review of ANDA ... ap-

plications." Pet. 26 (quoting 68 Fed. Reg. at 36,682). The decision below does not preclude FDA from requesting (or publishing) any information, and the agency's authority to enforce the Act has not been threatened, much less bewrenched.

C. The Challenged Use Code Is Correct

Even if petitioners could convince this Court to adopt an expansive reading of both "an approved use" and "patent information," petitioners would also have to prove that respondents' current use code narrative is incorrect. As the concurrence below explained, however, "there is nothing illegal, or even incorrect, about Novo's current use code." Pet. App. 21a. The counterclaim gives the district court no license to force Novo to choose between two truthful alternatives. Indeed, if the statute were so construed it would give rise to serious First Amendment problems. *See Hurley* v. *Irish-Am. Gay, Lesbian & Bisexual Group of Boston*, 515 U.S. 557, 579 (1995). In addition, petitioners would be unable to justify the issuance of such an order under the traditional criteria for equitable relief. *eBay Inc.* v. *MercExchange, L.L.C.*, 547 U.S. 388, 391 (2006).

The counterclaim places the burden of proof on the generic, and petitioners did not come close to proving that respondents' use code is incorrect. (The district court's conclusion in this respect was perforce vacated by the Federal Circuit.) Respondents explained at considerable length in the court below why their current use code narrative is accurate and entirely consistent with the Hatch-Waxman Act and all applicable regulatory guidance. Resp. C.A. Br. 34-41; Resp. C.A. Reply Br. 17-26; *see also* C.A. App. A679-A696. In short, FDA expressly allows a pioneer manufacturer to base its use code narrative on the approved method of use *or* indication for the

drug. 21 C.F.R. § 314.53(c)(2)(ii)(P)(1); *see also* Pet. App. 213a.

A use code that tracks the approved indication is entirely consistent with the Hatch-Waxman Act and its legislative history, which focus on indications. *See* H.R. Rep. No. 98-857, pt. 1, at 21 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2654. And there is no dispute that respondents' current use code narrative directly tracks the FDA-mandated indication for PRANDIN®. *Compare* C.A. App. A673 ("A method for improving glycemic control in adults with type 2 diabetes mellitus"), *with* C.A. App. A667-A668 (PRANDIN® is indicated for "improv[ing] glycemic control in adults with type 2 diabetes mellitus"). It therefore "alerts generics" such as petitioners to the existence of a patent that claims an approved use of repaglinide, discharging the notice function that is the objective of the patent listing requirements in the Hatch-Waxman Act. *See* Pet. 5-6. Because respondents' current use code narrative complies with all actual regulatory guidance, there is nothing for any court to "correct"—even if petitioners' construction of the statute were to be adopted.

As the majority and concurring opinions below recognized, petitioners' true grievance lies with FDA, not respondents. Pet. App. 14a, 20a. Petitioners' real complaint is that FDA rejected their section viii carve-out on the basis of its longstanding policy that an ANDA filer "must, despite any disagreement as to the correctness of the patent information, [submit] an appropriate certification for each listed patent." 21 C.F.R. § 314.53(f). They also disagree with FDA's regulatory decision to allow use codes that track approved indications. And petitioners are dissatisfied that FDA has elected to conserve its financial and experiential resources by declining to "police" most Orange Book submissions. *See ibid.*

Petitioners try to blame respondents for these regulatory determinations, but FDA decisions cannot be challenged or resolved in the context of a Hatch-Waxman counterclaim. Rather, petitioners must challenge FDA policies, including FDA's decision to deny their attempted section viii carve-out, by proceeding against FDA, in the appropriate forum, under the Administrative Procedure Act. *See Andrx Pharms., Inc.* v. *Biovail Corp.*, 276 F.3d 1368, 1379 (Fed. Cir. 2002). Petitioners concede that they *could* have challenged FDA's refusal to authorize their section viii carve-out (Pet. 20), but—for reasons they have never explained—petitioners have elected not to bring an APA suit against FDA. Nonetheless, the admitted availability of such a suit destroys the argument, advanced by petitioners and echoed by their *amici*, that the decision below "leav[es] generics without any [judicial] remedy." Pet. 3.

The court below ruled only that the Hatch-Waxman counterclaim is not available to petitioners on the peculiar facts of this particular case, which is not an issue that warrants this Court's attention.

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted.

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February 25, 2011

APPENDIX

APPENDIX A

UNITED STATES DISTRICT COURT FOR THE EASTERN DISTRICT OF MICHIGAN SOUTHERN DIVISION

NOVO NORDISK A/S and NOVO NORDISK, INC., Plaintiffs,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD., Defendants.

Case No. 05-40188
HON. AVERN COHN

* * *

MEMORANDUM AND ORDER DENYING PLAINTIFFS' MOTION TO DISMISS FOR LACK OF JURISDICTION[1]

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[1] Ordinarily, the Court would hold a hearing on this matter. However, upon review of the parties' papers, the Court finds that oral argument is not necessary. *See* E.D. Mich. LR 7.1(f)(2).

I.

This is a patent case. It involves the diabetes drug repaglinide marketed by plaintiffs Novo Nordisk A/S and Novo Nordisk, Inc. (Novo) under the trade name Prandin. Novo's patent for repaglinide, U.S. Pat. No. RE37,035 (the '035 patent), expired on March 14, 2009. Novo also holds a patent on the combination of repaglinide and metformin, U.S. Pat. No. 6,677,358B1 (the '358 patent) which does not expire until 2018. As will be explained, this case began in 2005 when Novo sued Caraco Pharmaceutical Laboratories, Ltd. (Caraco) and Sun Pharmaceutical Industries, Inc. (Sun) claiming infringement of the '358 patent when Caraco applied to the FDA to market a generic version of repaglinide. Caraco and Sun countersued for declaratory relief, raising issues including validity, enforceability, and misuse.

After five years of litigation, one appeal, and a three-week bench trial on the issues of patent validity and enforceability, a decision on which is pending, Novo has moved to dismiss the case for lack of subject matter jurisdiction. Although Novo alleged in its complaint that an actual controversy existed because of Caraco's conduct before the FDA, it now says that jurisdiction is lacking because of Caraco's later actions before the FDA. For the reasons that follow, Novo's motion is DENIED.

II.

In analyzing jurisdictional questions in declaratory judgment actions, there is no bright-line rule. *MedImmune Inc. v. Genentech Inc.*, 549 U.S. 118, 127 S.Ct. 764, 771, 166 L. Ed. 2d 604 (2007). Instead, "the question in each case is whether the facts al-

leged, under all the circumstances, show that there is a substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment." *Id.*

A party claiming declaratory judgment jurisdiction has the burden to establish the existence of such jurisdiction. *See Benitec Austl., Ltd. v. Nucleonics, Inc.*, 495 F.3d 1340, 1344 (Fed. Cir. 2007).

III.

The background of the case, including the process of certification of a generic drug, is described in several decisions of the Court reported at 450 F. Supp. 2d 757 (E.D. Mich. 2006) and 649 F. Supp. 2d 661, 2009 WL 2769855 (E.D. Mich. 2009). Background is also set forth in the Court of Appeals for the Federal Circuit's decisions reported at 601 F.3d 1359 (Fed. Cir. 2010) and 615 F.3d 1374, 2010 U.S. App. LEXIS 15611, 2010 WL 2990968 (Fed. Cir. July 29, 2010). What follows is background relevant to the instant motion.

A.

First, as to the statutory framework, this case falls under the Hatch-Waxman Act, which amended the Federal Food, Drug, and Cosmetic Act, Pub.L. No. 52-675, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301 et seq. (1994)) (the "FDCA"). Under the FDCA, the FDA is responsible for determining whether a generic drug product should be approved for sale to the public. 21 U.S.C. § 355(a). Under Hatch-Waxman, a pharmaceutical manufacturer, such as Caraco, seeking expedited FDA approval to market a generic version of a pat-

ented drug may submit an abbreviated new drug application ("ANDA"). 21 U.S.C. § 355(j). An applicant submitting an ANDA must certify one of four things: (1) that the drug for which the ANDA is submitted has not been patented (a "paragraph I" certification); (2) that any patent on such drug has expired (a "paragraph II" certification); (3) the date on which the patent on such drug will expire, if it has not yet expired (a "paragraph III" certification); or (4) that the patent on such drug "is invalid or that it will not be infringed by the manufacture, use, or sale of the new drug" for which the ANDA is submitted (a "paragraph IV" certification). 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV).

When an applicant submits an ANDA that contains a paragraph IV certification, it must give the owner of the relevant patent notice of the certification. 21 U.S.C. § 355(j)(2)(B). Importantly, inclusion of a paragraph IV certification in an ANDA is deemed an act of infringement. The statute, referring to an ANDA containing a paragraph IV certification, states: "It shall be an act of infringement" to submit an application under 21 U.S.C. § 355(j) "for a drug claimed in a patent . . . if the purpose of such submission is to obtain approval . . . to engage in the commercial manufacture, use, or sale of [the] drug . . . before the expiration of [the] patent." 35 U.S.C.A. § 271 (e)(2)(A).

If the ANDA contains a paragraph IV certification, and all applicable scientific and regulatory requirements have been met, approval of the ANDA "shall be made effective immediately" unless the patent owner brings an action for infringement under 35 U.S.C.A. § 271(e)(2)(A) within forty-five days of re-

ceiving the notice required by 21 U.S.C. § 355(j)(2)(B). 21 U.S.C. § 355(j)(4)(B)(iii). Hatch-Waxman further provides that, when a patent owner brings a section 271(e)(2)(A) infringement action, the FDA must suspend approval of the ANDA. *Id.* The suspension continues—and the FDA cannot approve the ANDA—until the earliest of three dates: (I) if the court decides that the patent is invalid or not infringed, the date of the court's decision; (ii) if the court decides that the patent has been infringed, the date that the patent expires; or (iii) subject to modification by the court, the date that is thirty months from the patent owner's receipt of notice of the filing of the paragraph IV certification. 21 U.S.C. § 355(j)(4)(B)(iii)(I)-(III); 35 U.S.C.[] § 271(e)(4)(A).

However, "the four types of certifications enumerated in 21 U.S.C. § 355(j)(2)(A)(vii) are not the only mechanisms by which an ANDA applicant can address a potentially relevant patent." *Apotex, Inc. v. Food & Drug Administration,* 393 F.3d 210, 213-14, 364 U.S. App. D.C. 187 (D.C. Cir. 2004). Rather than submit a paragraph IV Certification, an ANDA applicant may instead represent that it is not seeking approval for the patented method of use. 21 U.S.C. § 355(j)(2)(A) (viii). In what is commonly referred to as a "section viii statement", the ANDA applicant asserts that the "patent is inapplicable to the indication for which the drug product will be marketed." *In re Neurontin Antitrust Litigation,* No. 02-1390(FSH), 2009 U.S. Dist. LEXIS 77475, 2009 WL 2751029, [at] *2 n.11 (D.N.J. Aug. 28, 2009) (citing 21 U.S.C. § 355(j)(2)(A)(viii)).

In *Purepac Pharmaceutical Co. v. Thompson,* 354 F.3d 877, 880, 359 U.S. App. D.C. 319 (D.C. Cir.

2004), the D.C. Circuit explained the differences between a paragraph IV certification and a section viii statement as follows:

> A section viii statement indicates that a patent poses no bar to approval of an ANDA because the applicant seeks to market the drug for a use other than the one encompassed by the patent. *See* 21 U.S.C. § 355(j)(2)(A)(viii). For example, if a brand-name manufacturer's patent covers a drug's use for treating depression, and the ANDA applicant seeks approval to use the drug to treat any other condition, then a section viii statement would be appropriate. Thus, whereas applicants use paragraph IV certifications to challenge the validity of admittedly applicable patents, they use section viii statements to assert that patents do not apply. The FDA has long required that for every patent ANDA applicants use either a paragraph IV certification or a section viii statement—they may not use both. As the FDA puts it, "either the applicant is seeking approval for the use claimed in the patent, or it is not." *TorPharm, Inc. v. Thompson*, 260 F. Supp. 2d 69, 77 (D.D.C. 2003) (quoting the record in that case) (internal quotation marks omitted).
>
> Paragraph IV certifications and section viii statements have quite different consequences. Applicants submitting section viii statements have no obligation to provide notice, nor must they wait thirty months for FDA approval. . . . "[T]he FDA may [thus]

> approve a section viii application immediately, making it an attractive route for generic manufacturers, even though a section viii statement does not entitle a successful applicant to the 180-day period of exclusivity bestowed on paragraph IV applicants."

354 F.3d at 880 (quoting *Purepac Pharmaceutical Co. v. Thompson*, 238 F. Supp. 2d 191, 195 (D.D.C[.] 2002)). Finally, a section viii statement, unlike a paragraph IV certification, does not constitute an act of infringement sufficient to invoke subject matter jurisdiction under Hatch-Waxman. *See Purepac*, 238 F. Supp. 2d at 195.

B.

Second, as to the facts of this case, in February 2005, Caraco submitted an ANDA, seeking to market a generic version of repaglinide. Caraco included in its ANDA a "paragraph IV certification" stating that all five claims of the '358 patent were invalid and thus not infringed by Caraco's attempt to manufacture a generic repaglinide.

On April 2, 2005, the FDA acknowledged receipt of Caraco's ADNA and Paragraph IV certification. *See* Ex. 16 of Joint Appendix. Caraco also notified Novo of the certification as required.

In June 2005, Novo sued Caraco for infringement and later added Sun as a defendant. Novo claimed that Caraco's anticipated manufacture of repaglinide would infringe the '358 patent because the label would suggest the use of repaglinide with metformin. Both Caraco and Sun counterclaimed that the '358 patent was invalid, unenforceable, and would not be infringed by the sale of generic repaglinide.

Meanwhile, in August 2007, the FDA notified Caraco that its ADNA had been "tentatively approved." In the correspondence, the FDA noted that because there was a patent dispute involving the '358 patent, Caraco's application could not be finally approved. The FDA specifically referenced the lawsuit filed by Novo against Caraco. Ex. 21 of Joint Appendix.

On April 2, 2008, Caraco submitted an amendment to its ADNA, proposing that it be allowed to redact references in its label to the combination of repaglinide with metformin. In this filing, Caraco was attempting to submit a split certification, encompassing both a paragraph IV certification and a section viii certification. As noted in the Federal Circuit's decision:

> . . . at the FDA's urging [Caraco] sought a paragraph IV certification as to the drug product claims of the '358 patent, *and* a section viii certification as to the method claim.

Novo v. Caraco, 601 F.3d at 1379 n.16 (Dyk, dissenting) (emphasis added). *See also* Ex. 10 of Joint Appendix.

This point is critical inasmuch as Novo's motion is grounded on the premise that in seeking the amendment with the section viii certification, Caraco "dropped" its paragraph IV certification and, in so doing, the basis for subject matter jurisdiction was lost. This is a faulty premise. Novo did not abandon, drop, replace or otherwise waive the paragraph IV certification. This is clear when the record is further examined.

In May 2009, Novo submitted an amended use code for the '358 patent which the FDA approved.[2] Specifically, Novo changed the use code from "U-546–use of repaglinide in combination with metformin to lower blood glucose" to "U-968–a method for improving glycemic control in adults with type 2 diabetes mellitus." As the case history shows, the propriety of Novo changing the use code was hotly litigated with Novo eventually prevailing in the Federal Circuit.

The FDA then notified Caraco that it would not approve a section viii statement in light of Novo's amended use code. The FDA later instructed Caraco to change its ADNA to add back in the information about the combination of repaglinide and metformin, which essentially mooted Caraco's efforts at a section viii statement.

All of this is spelled out in a May 26, 2010 letter from Caraco to the FDA in which Caraco states in relevant part:

> . . . it is Caraco's understanding that FDA has currently decided to reject the proposed section viii statement with regard to claim 4 of the '358 patent and, therefore the FDA is now deeming Caraco's ANDA to contain a

---

[2] Shortly after Caraco sought the amendment, on July 9, 2008, Novo filed its first motion to dismiss for lack of subject matter jurisdiction. Following a status conference, Novo withdrew the motion. Novo refiled the motion after the proofs were submitted in the validity trial. The Court has already commented on the peculiar circumstances of Novo's filing in the Memorandum and Order of September 16, 2010. *See* Doc. No. 503.

> paragraph IV certification as of the time of tentative approval. Caraco may ultimately need to maintain its paragraph IV certification as to all claims of the '358 patent to obtain final approval. However, it is currently maintaining that certification under protest.

Ex. 4 of Joint Appendix. While Novo says that these statements mean Caraco was trying to "revive" its paragraph IV certification, that is not the case. Rather, these statements merely reconfirm that Caraco was pursuing both a paragraph IV certification and a section viii statement with respect to the '358 patent. When the section viii statement was rejected (because Novo was successful in obtaining an amended use code), the paragraph IV certification was still in place. At that point, Caraco's ANDA contained only the paragraph IV certification, which Caraco has continued to pursue.

C.

In the end, the fact is that there has always been a substantial controversy between the parties over the '358 patent. Caraco's paragraph IV certification is still pending before the FDA. Caraco's filing of the ANDA was an act of infringement sufficient to invoke subject matter jurisdiction. That dispute continues to date.

SO ORDERED.

/s/ Avern Cohn

AVERN COHN

UNITED STATES DISTRICT JUDGE

Dated: October 6, 2010

APPENDIX B

UNITED STATES DISTRICT COURT FOR THE EASTERN DISTRICT OF MICHIGAN SOUTHERN DIVISION

NOVO NORDISK A/S and NOVO NORDISK, INC., Plaintiffs,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD., Defendants.

Case No. 05-40188
HON. AVERN COHN

* * *

DECISION

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Appendix I – Reports and Articles Referenced in Decision

Appendix II – PX 477A

I. INTRODUCTION

A. The Case

This is a patent case under the Hatch Waxman Act, 21 U.S.C. § 35[5], *et. seq*. The patent-in-suit, U.S. Patent No. 6,677,358B1, NIDDM REGIMEN (the '358 Patent) in the words of the abstract:

> . . . discloses a method of achieving improvement in glycemic control by combined use of repaglinide and metformin in NIDDM patients poorly controlled on metformin alone.

The patent is owned by assignment by plaintiffs Novo Nordisk A/S and Novo Nordisk, Inc. (Novo). Defendant, Caraco Pharmaceutical Laboratories, Ltd. (Caraco) asserts that Claim 4, the claim-in-suit of the '358 patent which reads

> A method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising ad-

> ministering to a patient in need of such treatment repaglinide in combination with metformin

is invalid as obvious and anticipated, and is unenforceable because of inequitable conduct and patent misuse.

Proceedings against defendant Sun Pharmaceutical Industries, Ltd., the second defendant of which Caraco is a partially owned subsidiary, have been stayed until further order of the Court (Doc. 346).

The issues of obviousness, anticipation and inequitable conduct were tried to the Court in June and August of 2010. The issue of patent misuse is the subject of a separate proceeding before the Court.

B. The Decision

For the reasons which follow, which constitute the findings of fact and conclusions of law required by Fed. R. Civ. P. 52(a), the Court finds that:

- The '358 Patent is not invalid because of anticipation
- The '358 Patent is invalid because of obviousness
- The '358 Patent is not enforceable because of inequitable conduct

II. BACKGROUND

A. Overview

This case has a long and complicated history. It began with the filing of a complaint by Novo charging Caraco with infringement of the '358 Patent on July 21, 2005 (Doc. 1), and Caraco responding with an answer and counterclaim asserting [the] invalidity and

unenforceability of the '358 Patent (Doc. 7). Since filing, the case has generated over 500 docket entries.

B. History

The history of the case is generally described in the following decisions of the Court and the Court of Appeals for the Federal Circuit as follows:

On August 31, 2009, the Court held that Caraco could challenge the incorrect use code narrative furnished by Novo for placement in the Orange Book maintained by the Food and Drug Administration on its application for approval of the new drug covered by the '358 Patent, and that Caraco could assert an affirmative defense to the charge of infringement because of this. *Novo v. Caraco*, 649 F. Supp. 2d 661 (E.D. Mich. 2009).

On September 24, 2009, the Court found that Novo improperly filed a use code narrative in its application for approval of the new drug. *Novo v. Caraco*, 656 F. Supp. 2d 729 (E.D. Mich. 2009).

On September 25, 2009, the Court entered an Order and Injunction (Doc. 423) requiring Novo to correct the use code narrative in the Orange Book.

On April 14, 2010, the Federal Circuit reversed the Order and Injunction, holding that a counterclaim such as filed by Caraco challenging the Orange Book listing was not available under Hatch Waxman. *Novo v. Caraco*, 601 F.3d 1359 (Fed. Cir. 2010). On July 21, 2010, rehearing was denied. *Novo v. Caraco*, 615 F.3d 1374 (Fed. Cir. 2010). On December 23, 2010, Caraco applied to the Supreme Court for *certiorari*.

On June 9, 2010, the Court found that the relevant date for prior art in the challenge to validity of the '358 Patent was October 29, 1996. *Novo v. Caraco*, 2010 U.S. Dist. LEXIS 56752, 2010 WL 2403041 (E.D. Mich. June 9, 2010)

On October 6, 2010, in a Memorandum and Order, the Court denied Novo's motion to dismiss the case for lack of subject matter jurisdiction premised on the grounds that Caraco had changed the nature of its Application For A New Drug (ANDA) with the Food and Drug Administration (FDA). *Novo v. Caraco*, 2010 U.S. Dist. LEXIS 106729, 2010 WL 3492727 (E.D. Mich. Oct. 6, 2010).

On September 09, 2009, Caraco stipulated that its ANDA filed with the FDA infringed the '358 Patent (Doc. 309). On August 24, 2010, in a Notice of Lodging of Stipulation of Infringement, the stipulation was reaffirmed (Doc. 489).

III. THE TRIAL

On April 23, 2010, the Court entered an order (Doc. 459) reversing the order of proofs at trial. The trial extended over 11 days in June and August of 2010.

A. The Witnesses

Fourteen witnesses, as named in the List of Trial Witnesses (Doc. 490) filed by the parties post-trial, testified. The witnesses' direct testimony for the most part was presented in narrative form (*see* Doc. 459). A brief description by name and general nature of testimony of the witness follows.

1. Caraco

Name	General Nature of Testimony
Domenico Accili (Accili)	Expert in the field of endocrinology and diabetes research. Accili expressed the opinion that claim 4 of the '358 patent was invalid as obvious, and that there was a lack of unexpected results when repaglinide was combined with metformin.
Marcello Pagano (Pagano)	Expert in the field of biostatistics. Pagano expressed the opinion that there was a lack of statistical validity in Novo's studies with respect to the combination of repaglinide with metformin.

2. Novo

Name	General Nature of Testimony
Robert Moses, M.D. (Moses)	Medical Director of an Australian research institute. Moses was one of the principal clinical investigators of a study of the combination of metformin and repaglinide (Moses Study)[1]. His

[1] Appendix I contains a list of reports and articles referenced in this Decision, including the Moses Study, noted above. The appendix lists (1) the exhibit number for the report or article,

	research data and results were the foundation of the examples reported in the '358 [patent].
Peter Müller, M.D. (Müller)	A research associate in Novo's research department in Denmark. Müller is the named inventor of the '358 patent. He designed the Moses Study to test the combination of repaglinide and metformin.
Andreas Pfeiffer, M.D. (Pfeiffer)	A clinical specialist in the field of endocrinology. Pfeiffer conducted clinical research on the combination of repaglinide and metformin (Pfeiffer Study). He expressed the opinion that the results of the combination were unexpected.
Jeppe Sturis, Ph.D. (Sturis)	A principal scientist of Novo in Denmark. Sturis tested a combination of repaglinide and metformin in Zucker obese rats (Sturis Study). He expressed the opinion that the results of his testing were synergistic. The results were cited to the

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[Footnote continued from previous page]

(2) the full citation for the report or article, and (3) the Court's abbreviation for the report or article.

	Patent Office in support of patentability of the combination of repaglinide and metformin.
Howard Thaler, Ph.D. (Thaler)	An expert in biostatistics. Thaler reviewed the results of the Moses Study and the Sturis Study. He expressed the opinion that the studies showed synergistic results from the combination of repaglinide and metformin.
Peter Damsbo, M.D. (Damsbo)	Novo's chief medical advisor. Damsbo's early work with repaglinide provided a foundation for a therapeutic approach for the combination of repaglinide and metformin.
John Miller, M.D. (Miller)	Medical director of Novo in Australia. Miller coordinated and supervised the Moses Study. He described this work and said he was surprised by the results.
Michael Mark, Ph.D. (Mark)	A German scientist. Mark discovered repaglinide and attempted to commercialize it. He was involved in its transfer to Novo.
Arne Melander, M.D. (Melander)	Researcher in the clinical pharmacology of diabetes.

	Melander expressed the opinion that repaglinide was not interchangeable with sulfonylureas, and was not thought suitable for combination therapy with metformin.
Brian Reisetter, Ph.D. (Reisetter)	An expert in medical marketing. Reisetter expressed an opinion about the commercial success of the repaglinide-metformin combination therapy.
Alan Garber, M.D., Ph.D. (Garber)	An expert in clinical endocrinology and biochemistry. Garber expressed the opinion that claim 4 the '358 Patent is valid as nonobvious.
Bharati Nadkarni (Nadkarni)	A senior manager at Sun Pharmaceutical. Nadkarni described Sun's activities in India and Mynamar with repaglinide and sulfonylureas.

B. Exhibits

Roughly over 360 exhibits were introduced in evidence at trial. A consolidated list of trial exhibits (Doc. 494) was filed by the parties post-trial. The exhibits beyond the '358 Patent (JX 1) and an abbreviated File History (JX 2A), include correspondence, chains of e-mails, articles, abstracts of articles, clinical trials reports, curriculum vitaes of scientific witnesses, data compilations and various graphic com-

parisons, as well as a miscellany of other written material.

IV. THE LAW

A. Anticipation

Anticipation exists only if, within the four corners of a single prior art document, every element of the claimed invention is described, expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation. *Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1346 (Fed. Cir. 2009).

B. Obviousness

A patent is presumed valid, 35 U.S.C. § 282, and a party challenging its validity bears the burden of proving the factual elements of invalidity by clear and convincing evidence. *Pfizer v. Apotex*, 480 F.3d 1348, 1359 (Fed. Cir. 2007). Once the challenger has presented a prima facie case of invalidity, the patent owner has the burden of going forward with rebuttal evidence. *Id.* at 1360. This requirement "does not in substance shift the burden of persuasion, because the presumption of validity remains intact and the ultimate burden of proving invalidity remains with the challenger throughout the litigation." *Id.* (case citations omitted).

Where the accused infringer relies only upon prior art considered by the patent examiner, the statutory presumption of validity includes deference to the examiner's decision based upon the Patent Office's expertise. *American Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1359-60 (Fed. Cir. 1984). In the Supreme Court's *KSR* decision, where the invalidity

defense was based on prior art not considered by the Patent Office, the Court observed that "the rationale underlying the presumption – that the PTO, in its expertise, has approved the claim – seems much diminished here."[2] *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 426, 127 S. Ct. 1727, 167 L. Ed. 2d 705 (2007).

A valid patent may not be granted or upheld when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). The ultimate question of patent validity is one of law, based on an underlying factual framework laid out by the Supreme Court in *Graham v. John Deere Co.*:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved

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[2] On November 29, 2010, the Supreme Court granted *certiorari* in *i4i Ltd. Partnership v. Microsoft Corp.*, 598 F.3d 831 (Fed. Cir. 2010) on the question whether the clear and convincing standard must be applied to the invalidity defense under these circumstances. *Microsoft Corp. v. i4i Ltd.* Partnership, 131 S. Ct. 647, 178 L. Ed. 2d 476 (2010).

> needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966).

Often, as here, it is necessary to utilize this framework to determine whether a patent claiming a combination of elements known in the prior art was obvious at the time of the claimed invention. Over the years, the Federal Circuit created and applied a test known as the "teaching, suggestion or motivation" (TSM) test. Under this test, a patent claim is proved obvious only if a motivation or suggestion to combine the prior art teachings can be found in the prior art. The Supreme Court in *KSR* held that the TSM test can provide a "helpful insight," but noted that

> [o]ften, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. . . . As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court

> can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.

Continuing:

> The obviousness analysis cannot be confined by a formalistic conception of the words, teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way. In many fields it may be that there is little discussion of obvious techniques or combinations, and it often may be the case that market demand, rather than scientific literature, will drive design trends.

550 U.S. at 418-19.

Known disadvantages of prior art elements that might have taught away from the claimed combination may be taken into account in determining obviousness. *Id.* at 416, citing *United States v. Adams*, 383 U.S. 39, 51-52, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293 (1966).

In another step applicable here, *KSR* approved the selective use of the "obvious to try" test that had long been rejected by the Federal Circuit:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her

> technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421.

The Federal Circuit subsequently elaborated on the obvious-to-try "rule of thumb," identifying two factual situations where it was inappropriate:

> First, an invention would not have been obvious to try when the inventor would have had to try all possibilities in a field unreduced by direction of the prior art. When "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" an invention would not have been obvious. *[In re] O'Farrell*, 853 F.2d [894,] 903 [(Fed. Cir. 1988)]. This is another way to express the *KSR* prong requiring the field of search to be among a "finite number of identified" solutions. 550 U.S. at 421, 127 S.Ct. 1727; *see also Proctor & Gamble*, 566 F.3d at 996; *[In re] Kubin*, 561 F.3d [1351,] 1359 [(Fed. Cir. 2009)]. It is also consistent with our interpretation that KSR requires the number of options to be "small or easily traversed." *Ortho-McNeil Pharm., Inc. v. Mylan*

> *Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).
>
> Second, an invention is not obvious to try where vague prior art does not guide an inventor toward a particular solution. A finding of obviousness would not obtain where "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell*, 853 F.2d at 903. This expresses the same idea as the *KSR* requirement that the identified solutions be "predictable." 550 U.S. at 421, 127 S.Ct. 1727; *see also Proctor & Gamble,* 566 F.3d at 996-97; *Kubin*, 561 F.3d at 1359-60.

Bayer Schering Pharma AG v. Barr Labs, Inc., 575 F.3d 1341, 1347 (Fed. Cir. 2009). The Federal Circuit has declined to "cabin" the "obvious to try standard" to the "predictable arts" (as opposed to the relatively unpredictable biotechnology arts). *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009).

Where, as here, all the elements of the claimed invention are found in a combination of prior art references, the party challenging validity must show by clear and convincing evidence (1) that a skilled artisan would have had a reason or motivation to combine the teachings of the prior art to achieve the claimed invention combination, or would have found it obvious to try the claimed combination, and (2) that such person would have had a reasonable expec-

tation of success in doing so. *Pfizer v. Apotex*, 480 F.3d 1348, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 421.[3] The court in *Pfizer* elaborated on the "reasonable expectation of success":

> [C]ase law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success . . . [T]he expectation of success need only be reasonable, not absolute.

Id. at 1364.

A case of prima facie obviousness can be rebutted by "unexpected results," but "the results must be shown to be unexpected compared with the closest prior art." *Id.* at 1370. "[I]n order to properly evaluate whether a superior property was unexpected, the court should have considered what properties were expected." *Id.* at 1371. But even unexpectedly superior results may not be sufficient to overcome a strong prima facie case of obviousness. *Id.* at 1372.[4]

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[3] *Pfizer* was decided one month before *KSR*. In *KSR*, the Supreme Court held that the "obvious to try" standard may be applied in appropriate circumstances, as quoted above. 550 U.S. 398, 421, 127 S. Ct. 1727, 167 L. Ed. 2d 705 (2007).

[4] The parties have belabored the issue of whether the claimed combination produced synergistic, as well as unexpected and superior results. Synergy became part of the vocabulary in this case in an abstract written for publication describing the results of the Moses Study. *See*, DX 9; ¶ 96, *infra*.

The Supreme Court has endorsed the generally accepted definition of "synergistic," namely, "an effect greater than the sum of the several effects [of the constituent elements] taken separately." *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 282, 96 S.

See also, Wyers v. Master Lock Co., 616 F.3d 1231, 1246 (Fed. Cir. 2010).

A strongly contested legal issue here is the relevance and meaning of *Asyst Techs. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008), which Caraco relies upon for its holding that "objective evidence of non-obviousness [e.g., unexpected results and commercial success] must be commensurate in scope with the claims which the evidence is offered to support." Evidence of unexpected results, though based upon subject matter that lies within the scope of a patent claim, will not support the unobviousness of a claim whose breadth extends far beyond that evidence unless "the probative value of a narrow range of data can be reasonably extended to prove the unobviousness of a broader claimed range." *In re Clemens*, 622 F.2d 1029, 1036 (CCPA 1980); *see also* the MPEP § 716.02(d), which cites *Clemens; In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983) (cited in *Asyst*); *In re Tiffin*, 448 F.2d 791, 792, 58 C.C.P.A. 1420 (CCPA 1971) (cited in *Asyst*).

Prima facie obviousness can also be rebutted by evidence of commercial success of the claimed invention. *Graham, supra*, 383 U.S. at 17-18.

[Footnote continued from previous page]

Ct. 1532, 47 L. Ed. 2d 784 (1976). The Manual of Patent Examining Procedure (MPEP) states that "a greater than additive [i.e., synergistic] effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected." § 716.02(c).

C. Inequitable Conduct

The overall contours of the defense of patent unenforceability due to inequitable conduct have been summarized by Judge (now Chief Judge) Rader as follows:

> Applicants for patents have a duty to prosecute patent applications in the Patent Office with candor, good faith, and honesty; *see also* 37 C.F.R. § 1.56. A breach of this duty – including affirmative misrepresentations of material facts, failure to disclose material information, or submission of false material information – coupled with an intent to deceive, constitutes inequitable conduct. In determining whether inequitable conduct occurred, a trial court must determine whether the party asserting the inequitable conduct defense has shown by clear and convincing evidence that the alleged nondisclosure or misrepresentation occurred, that the nondisclosure or misrepresentation was material, and that the patent applicant acted with the intent to deceive the United States Patent and Trademark Office. The nondisclosure or misrepresentation must meet threshold levels of both materiality and intent. Once the threshold levels of materiality and intent have been established, the trial court must weigh materiality and intent to determine whether the equities warrant a conclusion that inequitable conduct occurred. *Id.* The more material the information misrepresented or withheld by the applicant, the less

> evidence of intent will be required in order to find inequitable conduct.

Honeywell Int'l Inc. v. Universal Avionics Sys. Corp., 488 F.3d 982, 999 (Fed. Cir. 2007) (internal citations omitted).

Even if a threshold level of both materiality and intent to deceive are proven by clear and convincing evidence, a court may still decline to render the patent unenforceable. *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1365 (Fed. Cir. 2008).

The applicable definitions of materiality and intent, however, are less settled.[5] "Materiality" is defined by the Patent Office's current rule as follows:

> (b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and
>
> > (1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or
> >
> > (2) It refutes, or is inconsistent with, a position the applicant takes in:

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[5] The Federal Circuit granted a petition for rehearing en banc in *Therasense, Inc. v. Becton, Dickinson and Co.*, 593 F.3d 1289 (Fed. Cir. 2010), and requested briefing on all aspects of the current framework for determining and balancing materiality and intent. *See* 374 Fed. Appx. 35 (Fed. Cir. 2010). Oral argument was held on November 9, 2010.

> ([i]) Opposing an argument of unpatentability relied on by the office, or
>
> (ii) Asserting an argument of patentability.
>
> A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

37 C.F.R. § 1.56(b) (2009).

The Federal Circuit has held that this current version, effective since 1992, was not intended to supplant the earlier "reasonable examine" standard or the case law interpreting it. *Digital Control v. Charles Machine Works*, 437 F.3d 1309, 1316 (Fed. Cir. 2006). The court further held that if a misstatement or omission is material under either test, or even under other previously applied tests, such as the "but for" test (the misrepresentation caused the examiner to approve claims he or she would not otherwise have approved) or the "but it may have" test (the misrepresentation may have influenced the examiner), then it is material. *Id.* at 1315-16. "To the extent that one standard requires a higher showing of materiality than another standard, the requisite

finding of intent may be lower." *Id.* In fact, recent Federal Circuit decisions have applied the definition from the earlier version of 37 C.F.R § 1.56, namely, information is material "where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent."[6]

Some decisions have found it appropriate, when weighing inferences relevant to intent, to consider plausible reasons for the withholding of material information:

> The intent element of the offense is . . . in the main proven by inferences drawn from facts, with the collection of inferences permitting a confident judgment that deceit has occurred. . . . however, inequitable conduct requires not intent to withhold, but rather intent to deceive. Intent to deceive cannot be inferred simply from the decision to withhold [information] where the reasons given for the withholding are plausible.

McKesson Information Solutions, Inc. v. Bridge Medical, Inc., 487 F.3d 897, 913 (Fed. Cir. 2007) (reasons for withholding prior art patent and information from related applications held insufficient to negate inference of deceptive intent).

> An inference of intent to deceive is generally appropriate, however, when (1) highly mate-

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[6] *E.g., Advanced Magnetic Closures, Inc. v. Rome Fastener Corp.*, 607 F.3d 817, 829 (2010); *Symantec Corp. v. Computer Assocs. Int'l*, 522 F.3d 1279, 1297 (2008).

> rial information is withheld; (2) "the applicant knew of the information [and] . . . knew or should have known of the materiality of the information; and (3) the applicant has not provided a credible explanation for the withholding."

Praxair, Inc. v. ATMI, Inc., 543 F.3d 1306, 1313-14 (Fed. Cir. 2008) (no good faith explanation given for failure to disclose material prior art).

Another 2008 decision of the Federal Circuit raises an additional hurdle for inferring deceptive intent when alternative inferences can be drawn from the evidence.

> We have also held that because direct evidence of deceptive intent is rarely available, such intent can be inferred from indirect and circumstantial evidence. But such evidence must still be clear and convincing, and inferences drawn from lesser evidence cannot satisfy the deceptive intent requirement. Further the inference must not only be based on sufficient evidence and be reasonable in light of that evidence, but it must also be the single most reasonable inference able to be drawn from the evidence to meet the clear and convincing standard.
>
> [internal citations omitted]

Star Scientific, *supra*, 537 F.3d at 1365 (emphasis added) (no deceptive intent found; withheld document found to be cumulative, and therefore not material). *See also, Advanced Magnetic Closures, supra*, 607 F.3d at 829. In *Star Scientific,* the Federal Circuit held that the existence of a reasonable alterna-

tive explanation completely precludes an inference of deceptive intent. A contemporaneous decision, however, gave the district court broad discretion to weigh the patentee's alternative explanations against the inference of deceptive intent, affirming a finding of deceptive intent, without imposing the "single most reasonable inference" standard. *Aventis Pharma S.A. v. Amphastar Pharmaceuticals, Inc.*, 525 F.3d 1334, 1344 (Fed. Cir. 2008) (failure to disclose that half life studies were done at different doses).

V. THE PATENT

A. Technical Overview

For ease of reference, in Parts V through VIII the paragraphs are numbered.

1. This overview is essentially based on the Glossary of Terms lodged with the Court on June 20, 2010 by the parties. This overview is a brief tutorial of the underlying technology.

2. One of the byproducts of the body's digestion of food is glucose (sugar), which enters the bloodstream. A persistently too high level of bloodstream glucose is termed hyperglycemia, while a persistently too low glucose level is called hypoglycemia. Insulin is a hormone produced by beta cells in the pancreas, where it is stored until rising blood glucose levels cause it to be released. Insulin instructs the body's cells to take up glucose from the blood for use as an energy source, and also instructs the liver to stop producing glucose and to instead take up glucose from the blood and store it as glycogen until needed by the body.

3. **Diabetes** is a glucose metabolism disorder characterized by hyperglycemia after meals and in the fasting state. About 24 million people in the United States have diabetes. Type I diabetes, represented by five percent of the diabetic population, occurs when the pancreas' beta cells fail to manufacture and secrete insulin in response to elevated blood glucose levels. The only therapy is treatment with exogenous (externally originated) insulin.

4. In **Type II diabetes**, representing the remaining 95 percent of the diabetic population, the beta cells fail to secrete sufficient insulin, and/or the body is resistant to the effects of insulin. Type II diabetes is also known as non-insulin dependent diabetes (NIDDM). It can be treated with orally administered antidiabetic drugs (**OADs**) in the form of monotherapy (a single OAD) or combination therapy (more than one OAD). **Insulin resistance** is a characteristic of Type II diabetes in which the cells and the liver are insensitive to the presence of insulin, and do not respond to the chemical message carried by insulin.

5. There are several groups of OADs. The two groups which are the primary focus of this lawsuit are insulin **secretagogues** and insulin **sensitizers**. The secretagogues stimulate insulin release from the pancreas' beta cells. Sensitizers reduce insulin resistance by acting on the liver to reduce glucose production from glycogen stored there, and improve insulin sensitivity in muscle and fat tissues.

6. Repaglinide,[7] one of the two ingredients specified in Claim 4 of the '358 Patent, is an insulin secretagogue. It is one of five members of the meglitinide class of secretagogues, only one other of which (nateglinide or A-4166) has been approved by the FDA. A second class of secretagogue consists of thirteen sulfonylureas.

7. Metformin, the other claimed ingredient in Claim 4, is an insulin sensitizer. It is the only one of three members of the **biguanide** class that has been approved by the FDA. A second class of sensitizer, the thiazolidinediones ("TZDs"), consists of five drugs.

8. Two measures of glucose control have been referred to in this lawsuit. The first is **HbA_{1c}** or glycosylated hemoglobin, a form of hemoglobin to which glucose in the blood binds. The glucose remains attached for the life of the hemoglobin cell (about four months). This parameter is not influenced by daily fluctuations in blood glucose, and shows the average glucose level in the recent past. It is therefore used to monitor the effect of diet, exercise and drug therapy on blood glucose. The second measure is **FPG** or **fasting plasma (blood) glucose**. This measurement is taken after a patient has not eaten for about

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[7] At the time this case was filed, repaglinide was a patented pharmaceutical, U.S. Patent No. RE37,035E (the '035 Patent). The patent expired on March 14, 2009. It was in anticipation of the expiration of the '035 Patent that Caraco filed the ANDA that precipitated the filing of this case by Novo and the counterclaim by Caraco which is the subject matter of this case and the trial.

eight hours (e.g., overnight). High levels of FPG can be caused by increased glucose production from glycogen stored in the liver, resulting from impaired insulin action in the liver.

9. As will be amplified below, combination therapy – using any two drugs having different mechanisms of action – will generally be more effective than monotherapy – using just one of those drugs. If monotherapy with a drug proves successful, a logical testing progression was to test that drug in combination therapy. Combination therapy using an insulin sensitizer and an insulin secretagogue was a well-known successful technique for treating Type II diabetes long before the invention claimed in the '358 Patent.

10. A combination of drugs is said to have an additive effect when the total effect equals the sum of the effect of each drug taken separately (e.g., Drugs A and B each reduce hypertension by 10% when administered separately, and reduce hypertension by 20% if administered together). If the combined effect exceeds the sum of the separately administered effects, the effect is said to be **greater-than-additive** or synergistic (e.g., Drugs A and B in the above example yield a 25% reduction in hypertension when administered together). If Drug B inhibits or counteracts the effect of Drug A, the drugs are said to be antagonistic (e.g., the combination of the same Drugs A and B reduce hypertension by only 5%).

B. Conception and Development of the Patented Combination

11. Novo is a large producer of drugs used to treat diabetes. In November, 1990, it acquired license rights to repaglinide, a known but still unapproved insulin secretagogue. Development of repaglinide became the exclusive focus of Müller, who joined Novo in Denmark as a clinical researcher in 1989. He is the patentee of the '358 Patent. During 1991-92, he treated Type II patients with repaglinide to determine proper dosages and prove its efficacy and safety. He also compared its performance with sulfonylureas, a well-known class of insulin secretagogues. 6/7/10 Tr. at 186-95 (Müller).[8]

12. As Müller explained, in that time period there were sulfonylureas (secretagogues) and metformin, an insulin sensitizer that had been around for many years. He conceived the repaglinide/metformin combination at an unknown date before June of 1994, and did not study any other repaglinide combinations. *Id.* 192, 198. He thought "it would make more sense" to combine repaglinide with metformin than with sulfonylureas, because of metformin's complementary mechanism of action. "That's why my thought was a good idea to combine those two." *Id.* at 192-93. Relative to patients whose glucose levels were not adequately controlled on metformin alone, he therefore "expected some additional improvements

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[8] References to the transcript will be cited in the following form: "Date, Tr. at __", followed by the witnesses name in parenthesis, where appropriate.

in the glucose control of the patients treated with the combination." 6/8/10 Tr. at 18 (Müller)

13. Damsbo, who worked with Müller, testified that metformin was the first drug they tested in combination with repaglinide because repaglinide "was a natural thing to combine with a sensitizer . . . it's not more complicated than that." 8/5/10 Tr. at 49 (Damsbo). That combination "was the only relevant other angle for treating Type II diabetes . . . apart from the sulfonylureas." *Id.* at 52. The sensitizer metformin was chosen because, by attacking the disease from different angles, "you might get a better effect, a synergistic effect." *Id.* at 54 [].

14. Müller had another reason for studying the effect of the repaglinide/metformin combination on patients that were not adequately controlled on metformin alone. While monotherapy with a new drug is necessary for regulatory review:

> you also try to keep a focus on how you can prove something new and exciting, not least for your marketing colleagues when they have to go out and sell your product after approval . . . [T]his would be an obvious – not obvious, but a good idea of where to expand your market . . . . It would be a scientifically sound thing to do. It would not cannibalize on the markets we were already looking for. So in that respect, I think it made sense.

6/8/10 Tr. at 13-14 (Müller).

15. The protocol for a clinical trial of the repaglinide/metformin combination on patients failing on metformin alone was developed under Müller's direc-

tion. *Id.* at 22. The study was conducted in Australia during 1995-96 by a team of investigators led by Moses. 8/5/10 Tr. at 201 (Miller).

16. On June 13, 1997, Novo filed a patent application on this combination therapy in Denmark, and filed a provisional application in the United States on October 29, 1997. The '358 patent was granted on January 13, 2004. The critical date for prior art under 35 U.S.C. § 102(b) is therefore October 29, 1996. The same critical date applies to prior art under § 102(b)/103. *See* Memorandum of June 9, 2010 (Doc. 417).

17. Claim 4, the only claim in suit, reads as follows:

> 4. A method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin.

C. Prosecution History

18. The patent examiner issued four successive rejections of Müller's application as obvious over the prior art. The first rejection was based upon a 1996 written by one of Novo's expert witnesses, Melander. (Melander Article).[9] The examiner stated:

> Melander teaches combination therapy as a rational approach to the treatment of NIDDM comprising administering agents that have different mechanisms of action and

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[9] *See* Appendix I and n.1, *supra*.

> different side-effect profiles. . . . One skilled in the diabetes art would have been motivated to combine two hypoglycemic agents as one pharmaceutical composition to treat NIDDM based on their onsets and durations of action in view of the teaching of Melander. Such would have been obvious in the absence of evidence to the contrary because it would have been reasonable to expect clinical efficacy to be additive, while dosage and side-effect profiles could be decreased, following the administration of clinically effective agents that demonstrate different modes of action.

JX 2A, Tab 3 at C0172889-90, Office Action dated 10/19/2000.

19. In response, Novo's argument included reliance on Example 3 of the application, which contains the data from the Moses Study, as demonstrating an unexpected "synergistic effect." *Id.* at Tab 4, C0172904-05, Amendment and Response filed 1/15/2002.

20. The examiner then repeated her obviousness rejection based upon the Melander Article and made the rejection [f]inal. *Id.* at Tab 6, C0172930-31, dated 3/15/2001.

21. Novo's next Amendment and Response argued that the Melander Article did not suggest the specific combination of repaglinide and metformin; that "obvious to try" is not a proper basis for rejection (KSR's endorsement of that basis had not yet occurred); and again argued that Example 3 in the application dem-

onstrated an unexpected synergistic effect. *Id.* at Tab 8, C0172937-39, dated 7/6/2001.

22. The examiner withdrew the Final Rejection because she entered an additional ground of rejection, not here relevant. She further stated that the claims failed to recite a synergistic effect in quantitative terms, and repeated her position that Melander's teaching made the claimed combination obvious. *Id.* at Tab 9, C0172944-45, dated 7/23/2001.

23. Novo then repeated its earlier arguments, adding that the law does not require that the improved or unexpected properties relied upon be included in the claims. *Id.* at Tab 11, C0172955-57, dated 1/15/2002.

24. A fourth and final obviousness rejection of all claims followed:

> The prior art is replete with examples of combination therapy wherein side-effects are minimized, dosages are reduced and a more clinically beneficial outcome is observed as compared with monotherapy [additional prior art publications omitted]. One skilled in the diabetic art would have been motivated to combine metformin for its longer acting effects and its ability to reduce blood glucose levels with a shorter acting, insulin-releasing agent having a rapid onset of action, in view of the teachings of Melander. Repaglinide and A-4166, which are more rapid in their onset of action and are shorter-acting, and are specifically disclosed by Melander, would have reasonably been preferable to the older sulfonylureas.

Id. at Tab 13, C0173001-02, dated 4/16/2002.

25. Novo's next Amendment and Response reiterated its "unexpected and synergistic effect" arguments, and submitted a Declaration of Sturis (Sturis Declaration, PX 233). The Sturis Declaration reported the results of his study of the repaglinide/metformin combination on Zucker obese rats,[10] and concluded that his data showed:

> . . . synergistic effects on glucose tolerance in Zucker obese rats and that this data, taken together with the data presented in Example 3 of the present application, strongly suggests that the combination of repaglinide and metformin has synergistic properties in type 2 diabetic patients.

Id. at Tab 14, C0173015, 10/16/2002.

26. Although the Sturis Declaration did not itself conclude that the test results were either unexpected or surprising, the accompanying Remarks of Novo's attorney, Dr. Richard Bork (Bork), asserted that the data contained in the application and in the Declaration "provides clear evidence of synergy . . . in the treatment of type II diabetes," and that any prima facie case of obviousness "is rebutted by the evidence of synergistic and surprising results achieved by the claimed combined therapy in humans." *Id.* at Tab 14, C0173010.

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[10] Zucker obese rats are a breed of rats specifically bred for use in research as models for obesity, diabetes and heart disease. *See* http://www.ratbehavior.org/RatSpecies.htm (last visited Jan. 13, 2011).

27. These submissions caused the examiner to withdraw her rejection of claims to the repaglinide/metformin combination. She unequivocally stated her reason:

> Based solely on the Declaration submitted by Dr. Sturis and reconsideration of the synergistic effects demonstrated in Example 3, pages 11-12 of the specification, and Table I, page 14, which are limited to the combination of metformin and repaglinide, this rejection of record is withdrawn for claims 25-29 and 31-33. Neither the Declaration nor the showing in the specification is directed to an unexpected synergistic effect resulting from the combination of compound AY4166 [nateglinide] and metformin. For the reasons of record, the rejection of record under 35 U.S.C. 103 is maintained with respect to claim 30.

Id. at Tab 17, C0173146. Although the examiner's first sentence is clear enough, the second sentence confirms that it was the presence or absence of evidence of the "unexpected synergistic effect" that was the sole basis of her decision. Although the examiner's first rejection opined that it was "reasonable to expect clinical efficacy to be additive" when drugs having differing modes of action were combined, the examiner cited no prior art describing or predicting synergistic (i.e., more than additive) results.

28. Additional Patent Office proceedings, not relevant to the issue of validity of Claim 4 in suit, followed the examiner's withdrawal of the rejection, and the '358 Patent issued on January 13, 2004. (JX 1).

Claim 4 corresponds to application claim 29, which was never amended during the prosecution of the application.

VI. ANTICIPATION

A. Discussion

29. Caraco contends that Claim 4 is anticipated by [ ]Rachman's 1995 article (Rachman). The article teaches the benefits of combination therapy for treatment of Type II diabetes, using insulin sensitizers and insulin secretagogues. It specifically identifies metformin as one of the first group and repaglinide as one of the second. Novo's expert, Garber, conceded that Rachman "suggests that metformin combined with repaglinide will give you additive effects [in diabetes patients]" 8/11/10 Tr. at 87 (Garber).

30. However, Rachman does not specifically describe the metformin/repaglinide combination in its listing of many individual drugs and drug types. The article also states that it is "uncertain" whether repaglinide will have clinical advantages, "and initial studies do not indicate a major effect" (Rachman at 471). Also, Rachman is listed in the '358 Patent as a reference that was considered by the examiner.

B. Conclusion

31. In sum, Rachman, though strongly probative on the issue of obviousness, does not fairly or directly teach the claimed metformin/repaglinide combination of Claim 4, and therefore does not anticipate Claim 4; the '358 patent is not invalid on grounds of anticipation.

VII. OBVIOUSNESS

A. Discussion

1. The Level of Skill in the Art

32. A person of ordinary skill in the art is a person having a medical degree with training in endocrinology and three years of clinical experience or laboratory research in the field of diabetes treatment. 6/1/10 Tr. at 100 (Accili). This definition, based on Accili's definition, is similar to Garber's except that the latter's definition would require that the three years of experience be in clinical treatment of diabetes. 8/10/10 Tr. at 109 (Garber). The inclusion of the alternative laboratory research experience is appropriate because excellent diabetes research on OADs has been done by laboratory researchers without clinical experience but having familiarity with OAD uses and combinations. 6/1/10 Tr. at 100 (Accili).

2. The Prior Art

33. The critical date for prior art under 35 U.S.C. § 102(b)/103 is October 29, 1996. *See*, ¶ 16, *supra*.

34. Garber testified that the prior art taught "two drugs are better than one" when they have "different mechanisms of actions" and attack diabetes from different angles. 8/11/10 Tr. at 51 (Garber). In response to the Court's question, Garber also agreed that "in general any two drugs which have different mechanisms of action are better than one." *Id.* at 53. Melander testified that the logical progression in testing new diabetes drugs is to test it in monotherapy, including comparison with other monotherapy drugs; then, if successful in monotherapy, in most

cases the "next logical step" is to test the drug in combination therapy. 8/9/10 Tr. at 183 (Melander).

35. The "most widely used and most extensively studied" OAD combination as of the critical date was metformin (an insulin sensitizer) combined with a sulfonylurea (a class of insulin secretagogues). (Consensus Statement at 1517); *see also* 6/1/10 Tr. at 125-26 (Accili). "[D]octors have been treating diabetes patients with combinations of metformin with secretagogues for about a half of a century." 8/11/10 Tr. at 44 (Garber). This combination had been prescribed both as separate and as co-formulated tablets. 6/1/10 Tr. at 128 (Accili); 8/11/10 Tr. at 44 (Garber).

36. The rationale for the metformin/secretagogue combination therapy is well summarized in the Melander Article[11] and was further explained by Accili at trial. Insulin secretagogues are OADs that act upon the pancreas' beta-cells to stimulate insulin secretion, thereby lowering blood glucose. OADs that reduce insulin resistance are "insulin sensitizers," because they increase receptivity of muscle and fat tissue to insulin's action. Thus, sensitizers improve glucose utilization by the body, and act on the liver to reduce glucose production there. 6/1/10 Tr. at 114-16 (Accili). Melander taught that if monotherapy with either of these types of drugs does not result in near-normal glucose levels:

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[11] The Melander Article was published in September, 1996, before the critical date, and is a survey of pre-1996 literature rather than an original study. 6/7/10 Tr. at 23-25 (Accili).

> [C]ombination treatment seems rational for a number of reasons. These agents have different mechanism of action and different side-effects; hence the clinical efficacy would be additive while dosage and side-effects could be minimized.

(Melander Article at 146).

37. Other prior art reported the beneficial effect of combination therapy using the sensitizer metformin with secretagogues such as the sulfonylureas, because of their different mechanisms of action. A 1965 article stated that "[t]he two drugs thus act synergistically, the sulphonylureas to augment release and plasma activity of insulin, and the diguanides [biguanides, such as metformin] to potentiate its effect on the tissues. . . . The *apparent synergistic* effect of the sulphonylureas and diguanides is probably due to their different modes of hypoglycaemic action." (Clarke at 1251) (emphasis added); 6/1/10 Tr. at 127 (Accili).

38. In 1995, the Consensus Statement reported that "the availability of agents that act by differing mechanisms or may have differing side effects permits the design of individualized regimens that address the heterogeneity of the pathophysiology of NIDDM." (Consensus Statement at 1515). After discussing sulfonylureas and metformin, the Consensus Statement observed that where glycemic goals are not maintained with an initial medication, "in most patients, it is reasonable to consider combination therapy." *Id.* at 1517. Further, "[t]he most widely used and most extensively studied combinations are a sulfonylurea plus metformin or a sulfonylurea plus

insulin." *Id. See also*, 6/1/10 Tr. at 125-26 and 148 (Accili).

39. Metformin is a member of the biguanide class, the oldest class of insulin sensitizers. Of the three members of that class known before the critical date, it was the only one currently available for clinical practice in most countries, the other two either having been withdrawn or never approved because of safety issues. 6/1/10 Tr. at 116 (Accili); Melander Article at 145. Metformin was approved by the FDA in 1995, and quickly became popular in the United States, both in monotherapy and combination therapy. 6/1/10 Tr. at 119 (Accili).

40. Two classes of insulin secretagogues were known before the critical date: sulfonylureas (used since the 1950s) and meglitinides (repaglinide and netaglinide). At that time, only the sulfonylureas were approved by a regulatory body for treatment of NIDDM. The Melander Article identified two new non-sulfonylurea "insulin-releasing drugs," then under study: repaglinide and A-4166 (netaglinide, repaglinide's sister meglitinide). He described them as having similar action to sulfonylureas, though absorbed and eliminated more quickly. Although they had not yet been approved, Melander said they "look very promising" because possibly less likely than sulfonylureas to cause dangerously low blood sugar levels. (Melander Article at 145). *See also*, 6/1/10 Tr. at 114-15 (Accili); 8/9/10 Tr. at 145 (Melander). Melander himself admitted at trial that his article would have encouraged a person of ordinary skill in the art to scientifically study the combination of repaglinide with metformin. 8/9/10 Tr. at 197 (Melander).

41. A 1995 article also encouraged combining OADs having different mechanisms of action, because "the limited efficacy of sulphonylureas and metformin on their own . . . make polypharmacy inevitable in many cases." (Rachman at 474). He added that it was "likely" that such therapy "will have additive effect." *Id.* at 467. The article specifically described repaglinide as a "non-sulphonylurea secretagogue." *Id.* at 471. Although Rachman did not specifically describe the repaglinide/metformin combination, Garber conceded that Rachman "suggests that metformin combined with repaglinide will give you additive effects [in diabetes patients]." 8/11/10 Tr. at 87 (Garber).

42. Further evidence of the state of the art as of the October 29, 1996 critical date is found in a November 12, 1996 publication (Kaku). Although published two weeks after the critical date, Garber agreed that the article was "just recapping the prior art" and that it had been written and submitted for publication 2-6 months earlier.[12] 8/11/10 Tr. at 78, 83-84 (Garber). Kaku described repaglinide as a "new insulin secretagogue" that is rapid and short-acting, and stated that "it is expected to be used" to improve postprandial hyperglycemia and to reduce delayed hypoglycemia (Kaku at NOVO-6741638). He also stated that that "combination therapy using these agents will be performed largely, because these

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[12] "The fact of near-simultaneous invention, though not determinative of statutory obviousness, is strong evidence of what constitutes the level of ordinary skill in the art." *Ecolochem, Inc. v. So. Cal. Edison Co.*, 227 F.3d 1361, 1379 (Fed. Cir. 2000).

agents have individual unique characteristics." *Id.* at NOVO-6741641. Figure 2 of the article displayed secretagogues as being combined with biguanide sensitizers (such as metformin). *Id.* at NOVO-6741644.

43. Garber acknowledged that, before the critical date, one of ordinary skill in the art "may" have considered repaglinide an appropriate candidate for combination therapy for at least some patient populations (namely, those whose "post-prandial," or after-meal, glucose levels were not under control.) 8/11/10 Tr. at 94 (Garber).

44. As part of the argument that it would not have been obvious to try combining repaglinide with metformin, Novo asserted that in 1996 there were at least 44 known OADs that provide at least 900 possible two-drug OAD combinations. *See* PX 477. This list includes seven insulin sensitizers (one biguanide, i.e., metformin and six TZDs), twenty insulin secretagogues (fifteen sulfonylureas and five meglitinides, including repaglinide), five glucose absorption inhibitors, six gluconeogenesis inhibitors and six weight-loss agents. Appropriately, Novo listed but did not count among the 44 OADs two other biguanides that were widely recognized as unsafe.

45. Accili, however, disagreed that each of these 44 OADs was appropriate for treatment of Type II diabetes. He considered the list "the proverbial kitchen sink," including drugs whose use would be considered malpractice. He named seven of the 44 that he could not in good conscience prescribe to anyone. 6/3/10 Tr. at 21 (Accili). In response to the Court's questions, Accili stated that Novo's expanded list included drugs that had been considered as po-

tential OADs at some time before 1996, but had been "totally discredited" by 1996. *Id.* at 21-22. He gave specific reasons, such as limited efficacy, discontinued availability, toxicity or other concerns for long-term safety. *Id.* at 8-13, 18, 24. Even Garber admitted that there were "no reputable weight-loss agents" due to "either limited efficacy or . . . concerns about their long-term safety." 8/11/10 Tr. at 75 (Garber). Similarly, he admitted that development of gluconeogenesis inhibitors "had been hampered by toxicity," and that none had reached the market even as of today. *Id.*

46. Later, again in response to the Court's questions, Accili stated that Novo's expanded list was the "potential universe" but it would have to be modified to show the "effective universe." 6/7/10 Tr. at 22-23 (Accili). At the Court's request, Accili prepared a chart showing the effective universe of OAD drugs. PX 477A, a copy of which is found in Appendix II. The chart lists (1) five sensitizers, including one biguanide (metformin) and four TZDs; (2) nine insulin secretagogues, including seven sulfonylureas and two meglitinides (repaglinide and nateglinide); and two glucose absorption inhibitors. As of the critical date, the TZDs were still in the testing stage, some having been withdrawn. Only two were considered viable, and none was approved by the FDA until 1997. 6/1/10 Tr. at 119 (Accili). Glucose absorption inhibitors interfere with the conversion of carbohydrates to glucose in the small intestine. As of the critical date it was known that this class of drugs does not directly treat either of the two causes of NIDDM, i.e., decreased insulin secretion or impaired insulin action. One of these, acerbose, was used be-

fore the critical date, but was known to have a modest effect relative to metformin and the sulfonylureas. 6/1/10 Tr. at 119-20 (Accili).

47. According to the Consensus Statement, the metformin/sulfonylurea combinations had already been widely studied and used, and several other potential combinations had been examined and used to a lesser extent. Consensus Statement at 1517. Thus, the untested candidates for combination therapy represented only a fraction of the seventeen OADs comprising the effective universe charted on PX 477A. Melander explained that it would have been "more interesting scientifically and clinically to examine combination therapies with metformin and repaglinide," as well as some others, than the already studied combinations of metformin and sulfonylureas. 8/9/10 Tr. at 195-96 (Melander).

48. Accili's testimony regarding the effective universe of candidates for combination therapy was credible. As of the critical date, this universe of potential or previously combined OADs included a "finite number of identified, predictable solutions." *KSR, supra.* The guidance provided by the prior art's teaching of the benefits of combining insulin secretagogues and insulin sensitizers created a reasonable expectation of success in achieving at least additive results from combination of these candidate OADs. *See Bayer Schering* and *Pfizer, supra*. In other words, the Court is not persuaded by Novo's argument that it was not obvious by the prior art to try combining repaglinide and metformin. Indeed, as explained above and below, quite the opposite was true.

49. Novo also asserts that prima facie obviousness is precluded because the prior art taught away from the claimed combination. Specifically, repaglinide was known to have a small impact on fasting plasma glucose (FPG) due to its short biological activity life.

50. According to Melander[,] because repaglinide was quick-acting and quickly eliminated from the body, it was viewed as a "niche compound" useful for only a "narrow and very specific patient population." 8/9/10 Tr. at 84 (Melander). However, Melander's own article, after citing these properties, stated that repaglinide would lessen certain risks and looked "very promising." (Melander Article at 145). He also admitted that his article taught that a short-acting sulfonylurea (glipizide) could be combined with metformin in some circumstances, without problem; that all sulfonylureas, in principle, achieve the same results; that "sulfonylurea and repaglinide are alternatives if you're looking for an insulin secretagogue;" and that the article encouraged a person of ordinary skill to study the metformin/repaglinide combination. 8/9/10 Tr. at 177-78, 182, 193-94, 197-98 (Melander); *see also* 8/11/10 Tr. at 64-66 (Garber). And Garber admitted that even if repaglinide were not beneficial for high-FPG patients, Rachman still suggested that its combination with metformin could produce additive effects and be useful for patients with elevated post-prandial glucose. *Id.* at 87, 94 (Garber); Rachman.

51. The examiner, as more fully quoted above (¶¶ 18, 24), also cited the Melander Article to support her view that rapid and short-acting repaglinide "would have reasonably been preferable to the older sulfonylureas" for combination with longer-acting

metformin. PX 2A at Tab 13, C0173001-02, dated 4/16/2002.

52. In sum, the prior art as a whole did not teach away from combining repaglinide with metformin, even if beneficial results might not be obtained for all Type II diabetes patients.

3. Prima Facie Obviousness

53. As presented in detail above, the record clearly and convincingly establishes that the prior art supplied the teaching, suggestion and motivation to combine repaglinide with metformin as combination therapy for Type II diabetes. The prior art taught that two drugs having different mechanisms of action in treating Type II diabetes are better than one.

54. The combination of metformin (an insulin sensitizer) and a sulfonylurea (a class of insulin secretagogues) had been widely studied and successfully used because of their differing mechanisms of action. This drug combination was the closest prior art. The prior art described the effect of this combination therapy as additive and synergistic.

55. Repaglinide was a known insulin secretagogue having a similar mechanism of action to sulfonylureas, especially the fast-acting sulfonylureas, and hence was known to have a different mechanism of action than metformin.

56. It was a logical testing progression to try combination therapy once monotherapy with a new drug (here, repaglinide) proved successful. Clinical efficacy would be additive while dosage and side-effects could be minimized.

57. Whether looking for a secretagogue to combine with metformin, or a sensitizer to combine with repaglinide, a finite number of identified predictable solutions existed among the OADs in the effective universe of candidates for combination therapy.

58. Metformin was the most widely used insulin sensitizer, and the only one available in most countries. The effective universe of insulin secretagogues to combine with it comprised a maximum of seven sulfonylureas (several of which had already been successfully so combined), and two new meglitinides (repaglinide and nateglinide).

59. The effective universe of insulin sensitizers to combine with repaglinide comprised a maximum of four TZDs and one biguanide (metformin, the most widely used sensitizer). This universe qualifies as a "finite number of identified, predictable solutions." *KSR*, 550 U.S. at 421.

60. Novo's experts admitted that the prior art suggested to persons of ordinary skill in the art that the combination of repaglinide and metformin be studied (Melander), and that such combination would produce additive effects in the control of glucose levels in Type II diabetes patients (Garber). There was a reasonable expectation of successful and beneficial results from the claimed combination, including reduction in HbA_{1c}, FPG and insulin resistance.

61. Market pressure motivated Müller to expand Novo's market for repaglinide by incorporating it in combination therapy as well as in monotherapy.

62. Müller, who was charged with developing repaglinide for the market, considered it a good idea to combine it with metformin because of their comple-

mentary mechanisms of action. He expected such combination therapy to provide additional improvement in glucose control for patients inadequately controlled on metformin alone.

63. Metformin was the first and only sensitizer chosen by Müller for combination therapy testing with repaglinide. His colleague, Damsbo, considered it the "natural" combination, and the only relevant angle for treatment other than a sulfonylurea.

64. These facts are reinforced by the repeated rulings of the examiner, quoted above, regarding the teaching, suggestion and motivation provided by the prior art, based primarily upon the same Melander Article. Significantly, the examiner did not have the benefit of the testimony Müller and Damsbo as to their motivation to make the claimed combination, and their expectations for its results. Those expectations were consistent with those taught by the prior art.

65. In view of these facts, established by clear and convincing evidence, a person of ordinary skill in the art, as of the critical date, would have found it obvious to try the combination of metformin with repaglinide as a potential treatment for Type II diabetes. As such, the Court finds that a prima facie case of obviousness exists.

4. Secondary Considerations

(a) Background and Relevant Precedents—Unexpected Results

66. Before reaching the ultimate conclusion on the issue of obviousness, the evidence and assertions of unexpected and surprising results, as well as syner-

gistic results, must be considered. The case law has sometimes referred to this factor as a "secondary" consideration, placing it in the category with commercial success, copying, failure of others and long-felt but unsolved need. These sources of evidence provide only an indirect bas[i]s for inferring nonobviousness, whereas the Court views evidence of surprising or expected properties as more direct and technological evidence bearing more directly on the statutory inquiry as to "the differences between the subject matter sought to be patented and the prior art."[13] 35 U.S.C. § 103(a). Because in patent law, "a compound and all of its properties are inseparable," evidence of the properties of the claimed compound is directly relevant to show what the claimed invention is. *In re Papesch*, 315 F.2d 381, 391, 50 C.C.P.A. 1084, 1963 Dec. Comm'r Pat. 334 (C.C.P.A 1963).

67. In response to a question by the Court, Novo's counsel provided a useful definition: "a surprising result or surprise in the context of this case would be if there is a result that is inconsistent with what was known in the art, inconsistent with an expectation of a person of skill in the art based on the literature or the accumulated knowledge . . . ." 8/5/10 Tr. at 29.

68. Two contrasting Federal Circuit decisions involving allegedly unexpected results provide a useful perspective and framing for the present issue. First, in *McNeil-PPC, Inc. v. L. Perrigo, Co.*, 337 F.3d 1362

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[13] On this and other points, the thorough and insightful analysis of Professor Rebecca S. Eisenberg in her article, *Pharma's Nonobvious Problem*, 12 LEWIS & CLARK L. REV. 375, 418 (2008) should be considered.

(Fed. Cir. 2003), McNeil was faced with the expiration of its patent on loperamide, the active ingredient in its best-selling antidiarrheal product. McNeil sought to patent an improvement to extend its market-leading position. *Id.* at 1364. The patent had composition and method claims drawn to loperamide (or one of a specified group of other antidiarrheal compounds) in combination with the known antiflatulent simethicone for the treatment of diarrhea and flatulence (gas). The prior art described many combinations of various antidiarrheal drugs with simethicone, and the court found it obvious to substitute loperamide in the combination with simethicone, *id.* at 1367). Thus, the Federal Circuit found the patents invalid. The Federal Circuit also found that the district court had properly discounted the secondary indicia of nonobviousness, in that McNeil had commercial motivation to make the combination; the evidence commercial success was obscured by massive advertising; and the proffered clinical studies were too inconsistent and lacking in appropriate comparative tests to demonstrate unexpected or synergistic effects. *Id.* at 1370.[14]

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[14] Caraco strongly relies on *Richardson-Vicks, Inc. v. Upjohn Co.*, et al, 122 F.3d 1476 (Fed. Cir. 1997), where obviousness was found, notwithstanding unexpected and unchallenged synergism. While that case has many factual similarities to the present case, a careful reading reveals that the only difference between the claimed combination and the prior art was that the same two prior art drugs that were claimed in the patent as a "combinatory immixture" (i.e., in a single tablet) had been prescribed together but as separate tablets. *Id.* at 1480, 1483-84. Relevant to the issue of claim scope discussed in Part VI(A)(4)(a)(iv), *infra*, the examiner allowed the claims only

69. In *Ortho-McNeil v. Mylan Laboratories*, 520 F.3d 1358 (Fed. Cir. 2008), the patent was directed to a new chemical compound that has had substantial commercial success as a significant epilepsy drug. The new compound was created as an intermediate byproduct in the course of the inventor's search for a new antidiabetes drug. The record showed that it was unlikely that a person of ordinary skill would have started with the formulation that the inventor started with; there were no clues as to what properties that the claimed intermediate might have; and no reason to interrupt the development process and test this intermediate "for properties far afield from the purpose for the development in the first place (epilepsy rather than diabetes)." *Id.* at 1364. The court observed that "this clearly is not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness. *Id.* The record also showed "powerful unexpected results," skepticism of experts, copying and commercial success. *Id.* at 1365. Accordingly, the Federal Circuit affirmed the holding of nonobviousness.[15]

[Footnote continued from previous page]

when a new claim set limited in scope to the specific dosages used in the synergy-proving tests was submitted. *Id.* at 1482. Thus, this case is not particularly illuminating to the issue at hand.

[15] Novo strongly relies upon *Sanofi-Synthelabo v. Apotex*, 550 F.3d 1075 (Fed. Cir. 2008), where nonobviousness was found. Unlike Müller's combination of two prior art drugs, following the roadmap of the prior art, the patent in *Sanofi* was on an entirely new compound for preventing blood-thrombotic

70. These cases illustrate that determining whether an unexpected result exists requires a detailed factual analysis of the trial record.

(b) The Trial Record—Unexpected Results

71. The question of unexpected and surprising results was extensively and vigorously contested by the experts at trial. All of them, including Garber, aided in an understanding of this complex subject matter. However, on the particular issue of unexpected results, Garber was frequently required to retreat from opinions expressed in his direct testimony when confronted by his earlier deposition testimony and his own and others' prior contradictory publications.

72. Although the examiner cited the Melander Article as suggesting that combination therapy should be additive, she cited no predictions or reports of synergistic results from the closest prior art. As noted above (¶ 27), the examiner ultimately withdrew her rejection of Claim 4 "solely" on the basis of the evidence of the unexpected synergistic effects of the claimed combination. However, the examiner:

[Footnote continued from previous page]

events such as heart attacks and strokes. It resulted from a very complex, costly and unpredictable process of separating components of a compound that itself had been the result of years of costly trial and error research. The physical properties of the separated components, even if they could be obtained, were not only unpredictable, but were most likely to have an unpredictable blend of beneficial and toxic properties. The component that became the subject of the patent had the "rare" characteristic of possessing only favorable activity and no toxicity. *Id.* at 1080-81, 1087-90. Thus, this case is not analogous.

- did not have the benefit of the testimony of Müller and Damsbo as to the results they expected (¶¶ 12-13, *supra*);
- was unaware that several prior art publications described or predicted synergistic results from combination therapy with metformin and secretagogues of the sulfonylurea type (¶¶ 71-75 *infra*);
- did not have the benefit of expert testimony concerning reasonable expectations for, and explanation of the results of, the claimed combination (¶¶ 34-36, 40-43, 50 *supra*; 83-85, *infra*);
- was unaware of the undisclosed conclusions of the Sturis Declaration (¶ 141, *infra*).

70. Repaglinide was known to have properties and effects similar to those of the sulfonylureas in the context of combination therapy. The teachings of several prior art or contemporaneous publications have been described above. (Melander Article, Rachman and Kaku). Moreover, the examiner herself observed that, because of its properties, repaglinide "would have reasonably been preferable to the older sulfonylureas" in combination with metformin. JX 2A at Tab 13, C0173002.

71. Indeed, a 1995 article discussing the results of clinical trials stated that the differing mechanisms of action of metformin and sulfonylureas "can be used alone or together to produce synergistic, if not complementary, actions in various clinical situations." "When metformin and sulfonylureas are used in dual therapy, there is an apparent synergy of action

Such synergy should produce adequate glycemic control in all but the most severe or advanced cases of NIDDM." Karlsson/Garber (DX 307 at 78, 81) (emphasis added).

72. Referring to the results of other clinical trials involving the diguanide (or biguanide) metformin and a sulfonylurea, Clarke, in 1965, *see*, ¶ 37, *supra*, states that "[t]he two drugs thus act synergistically, the sulphonylureas to augment release and plasma activity of insulin, and the diguanides to potentiate its effect on the tissues. . . . The apparent *synergistic* effect of the sulphonylureas and diguanides is probably due to their different modes of hypoglycaemic action." (Clark at C0173325[,] emphasis added).

73. A 1995 article by Novo's expert, Garber, states that:

> Combination therapy with both sulfonylureas and metformin is the next logical step to control NIDDM patients not adequately treated with either agent alone. Additive or synergistic action to control hyperglycemia should be anticipated . . . .

(Garber at 84[,] emphasis added).

74. Another 1995 article by Garber refers to the extensive clinical experience with metformin in Europe and Canada in the past 30 years, and states that "[i]t may also be used in combination with a sulfonylurea in patients not responding adequately to sulfonylurea or metformin monotherapy, because these agents work by different mechanisms and appear to have a *synergistic* effect when used concomitantly." (Garber II at 568, emphasis added, *see also* at 578-80).

75. Similarly, a 1995 Bristol-Myers Squibb Company product monograph describing its Glucophage brand metformin drug states that it is "synergistic in combination with a sulfonylurea." (Bristol-Myers at 3, emphasis added).

76. As of the critical date, a person of ordinary skill in the art would have reasonably expected success in the form of beneficial, and even synergistic, results in the control of glucose levels by combination therapy using metformin and repaglinide. This finding is based upon the evidence described above establishing that: (1) the closest prior art was combination therapy using metformin and a sulfonylurea; (2) combination therapy using metformin and one of the sulfonylurea class of secretagogues was well known in the art to produce beneficial and even synergistic results in controlling glucose levels in Type II diabetes patients; (3) repaglinide was known as an insulin secretagogue having a similar mechanism of action to the sulfonylurea class of secretagogues.

77. As part of its counterargument, Novo relies on three studies to support its claim of substantial and unexpected improvements in glucose control and insulin sensitivity resulting from metformin/repaglinide combination therapy: the Moses Study, that was the basis for data found in the '358 Patent, the Sturis Study, and the Pfeiffer Study. Each study is discussed in turn below.

(i) The Moses Study

78. For the Moses Study, patients failing on metformin monotherapy were chosen for the test population. One test parameter was HbA_{1c} or glycosylated hemoglobin, which shows the average glucose level in

the recent past. Combination therapy reduced that level by 1.41%, about twice the drop produced by the two monotherapy treatment results combined. 8/5/10 Tr. at 124 (Miller); Moses Study at table 8-1, Figure 8-1; top half of DX 393, page 2.

79. Novo particularly emphasizes the dramatic reductions in fasting plasma glucose (FPG) levels resulting from metformin/repaglinide combination therapy for the patients in the Moses Study. Novo's witnesses testified that little or no reduction in FPG was expected in patients who were failing on metformin monotherapy because of repaglinide's known short duration of action. 8/10/14 Tr. at 148 (Garber); 6/7/10 Tr. at 91, 97-98 (Moses). Yet the combination therapy test results showed a reduction in FPG of more than eight times the reduction achieved by metformin alone. (Moses Study at Table 8-3, Figure 8-2; top half of DX 393, page 1). This result was asserted to be even more surprising because achieved with lower repaglinide dosages than given to the repaglinide monotherapy patients in the study, i.e. an unexpected "dose-sparing effect."

80. Various Novo witnesses and documents described the Moses Study results as "suggestive" of synergy, or showing synergistic "effects" or "properties" in the metformin/repaglinide combination. These qualifications were appropriate, because it was agreed that the Moses Study was not designed to show, and could not show, statistically significant synergy because ethical reasons precluded removing the sick patients from all therapy in order to perform the required placebo-placebo control group arm of a more comprehensive test. *See[,] e.g.*, 6/7/10 Tr. at 120

(Pagano); 6/10/10 Tr. at 54-55 (Thaler); 6/7/10 Tr. at 89 (Moses).

81. Novo contends that, to this day, there is no explanation for the unexpected improvements in HbA_{1c} and FPG resulting from this combination therapy, and no explanation for the "dose-sparing effects" from such therapy.

82. However, the dispositive fact in this analysis of Novo's various study test results, however, is whether the results were unexpected, not whether they were suggestive of synergism or even statistically synergistic. *See* MPEP § 716.02(c), quoted in footnote 3, *supra*. If synergistic results were expected, they would not negate obviousness. Moreover, a convincing explanation for the Moses Study test results was offered at trial.

83. Accili explained that the patients in the Moses Study, chosen because they were failing on metformin monotherapy, were therefore experiencing the effects of glucose toxicity and insulin resistance, wherein the body resists insulin's action. 6/1/10 Tr. at 110-12 (Accili). In this condition, the pancreas no longer can compensate for this insulin resistance. Both post-prandial and fasting hyperglycemia result, the former because the body is unable to process glucose from the meal, and the latter because of increased glucose production by the liver resulting from impaired insulin action there. The resulting hyperglycemia is self-perpetuating and extremely dangerous. On the other hand, lowering hyperglycemia in such patients "jump-starts a virtuous cycle that tends to improve glucose metabolism." *Id.* at 111-12. *See also*, 8/1/10 Tr. at 141-43 (Garber).

84. The patients in the Moses Study had been suffering from uncontrolled glycemic levels for three years. 6/3/10 Tr. at 61-62 (Accili). The prior art taught that glucose toxicity interferes with any OAD's effectiveness, including metformin's ability to improve insulin sensitivity. And reducing glucose toxicity will increase insulin sensitivity. 8/11/10 Tr. at 142-44 (Garber). Garber admitted that the prior art Clark article taught that patients suffering from glucose toxicity, upon receiving combination therapy with metformin and an insulin secretagogue (a sulfonylurea in Clark's study), saw their glucose toxicity wane, allowing the metformin to work as it should to increase insulin sensitivity. That in turn lowered their fasting plasma glucose levels below what it had been with either drug alone. *Id.* at 139-44 (Garber); Clark.

85. Garber was not surprised by Clark's explanation for the increased insulin sensitivity, as that phenomenon was understood even before that prior art article. *Id.* at 140. Clark's conclusion supplies the explanation for the "unexpected" reductions in the HbA_{1c} and FPG level improvements in the patients in the Moses Study once the secretagogue repaglinide was combined with their formerly insufficient metformin therapy. The repaglinide "jump-started a virtuous cycle" that caused their glucose toxicity to wane so that the metformin could work.

86. Similarly, the result achieved by combination therapy on the patients in the Moses Study, using lower dosages of repaglinide than used in the monotherapy, was the known "dose-sparing" consequence of combination therapy. The examiner cited the Melander Article as support for her view that "[t]he

prior art is replete with examples of combination therapy wherein side-effects are minimized, dosages are reduced and a more clinically beneficial outcome is observed as compared with monotherapy." JX 2A, Tab 13, C0173001-02; Melander Article at 146; Hermann/Melander at 1107.

87. The evidence does not establish that the claimed combination therapy produces clinical results superior to those produced by the closest prior art. The evidence is to the contrary. Two prior art studies reported greater reductions in HbA_{1c} and FPG than those of the Moses Study. The Hermann/Melander study, using metformin and the sulfonylurea glyburide, yielded a 2.3% reduction in HbA_{1c} and 6.1 mmol/l reduction in fasting plasma glucose for patients inadequate controlled on metformin monotherapy; a 2.0% reduction in HbA_{1c} and 4.8 mmol/l reduction in fasting plasma glucose for patients inadequately controlled on glyburide monotherapy; and a 2.2% reduction in HbA_{1c} and 6.1 mmol/l reduction in fasting plasma glucose for naïve patients treated with the metformin/glyburide combination. Hermann/Melander, Table 4.

88. The DeFronzo study of the same metformin/glyburide combination yielded a 1.7% drop in HbA_{1c} and 3.5 mmol/l reduction in FPG. DeFronzo; 6/2/10 Tr. at 25 (Accili). These reductions are all greater than those of the Moses Study (a 1.4% reduction in HbA_{1c} and 2.18 mmol/l reduction in FPG).

89. The probative value of these comparative numerical results is challenged by Novo, because of differences in the patient populations and treatment parameters, and the associated expectations for the

treatments. Both Novo and Caraco have stressed the important role of the particular characteristics of various Type II diabetes patient sub-populations in predicting and explaining the results of OAD therapy. While these numerical comparisons may therefore not establish that clinical results of the claimed combination were inferior to those of the closest prior art, neither does the record contain any comparative test results establishing superiority of the claimed combination.

90. But there is other less challengeable evidence that is persuasive of the fact that the clinical efficacy of the claimed combination therapy is not superior to the efficacy of the closest prior art. First, Garber is a practicing physician who has spent his entire 35-year career focused on the treatment and management of diabetes, both treating patients and conducting clinical studies. 8/10/10 Tr. at 100-01 (Garber). Garber testified that he "rarely prescribe[d]" the claimed combination, and "the situations in which I would normally use repaglinide would not be situations in which I'd normally use metformin." 8/11/10 Tr. at 132, 134 (Garber). He also testified that he was "probably not" offering an opinion that the claimed combination is superior in terms of efficacy to the prior art metformin/sulfonylurea combination. *Id.* at 112-13.

91. Second, and by contrast, Accili has spent 24 years doing research in diabetes in academia, administrative agencies and clinical capacities. He also treats patients and supervises diabetes-related clinical trials. 6/1/10 Tr. at 95-96 (Accili). Accili testified that he prescribes combination therapy with metformin and sulfonylureas about 20 times more often

than with the metformin/repaglinide combination. 6/7/10 Tr. at 37.

92. Third and finally, a Novo-financed literature review published in 2008 discusses the Moses Study and Pfeiffer Study, along with studies of metformin/sulfonylurea combinations. The author concludes that "[c]ollectively, these data indicate that combination therapy with repaglinide plus metformin may provide efficacy *comparable* to other combinations plus a favorable safety profile in the early treatment of type 2 diabetes." Raskin, at 1172 (emphasis added). Thus, twelve years after the Moses Study, Raskin was unable to conclude that the claimed combination produced results superior to those provided by the closest prior art.

93. These specific examples are reinforced by the overall market's reaction to the claimed combination. As presented more fully in Part VII(A)(4)(c) Commercial Success, *infra*, only a small and declining percentage of Type II diabetes patients taking OADs are taking the claimed combination therapy. The record as a whole therefore does not support a conclusion that the claimed combination yields superior results to those of the closest prior art.

94. Notwithstanding that several Novo witnesses testified as to their surprise at the Moses Study results, the weight of published prior art and expert testimony compels the conclusion that one of ordinary skill in the art should have expected successful, and perhaps even synergistic, results from the combination therapy given to the patients in the Moses Study.

95. Further, the trial testimony in 2010 of Novo's witnesses proclaiming their surprise in 19[9]6 concerning the unexpected and "synergistic" results of the Moses Study is unsupported by contemporaneous documents. The 1996 Clinical Trial Report of the Moses Study, signed by Moses, stated that the combination therapy "produced statistically superior glycemic control" compared to monotherapy with the two constituent drugs. There is no mention of synergism or even suggestions of synergistic effects in the Report. Nor does the Moses Study use the words "unexpected" or "surprising" anywhere in its discussion of Efficacy Results, Conclusions, Efficacy Evaluation, Efficacy Conclusions, Discussion, Overall Conclusions or anywhere else. Miller, who supervised all of Novo's clinical studies in Australia, testified in response to the Court's question that he did not know of any contemporaneous Novo document that mentioned synergism. 8/5/10 Tr. at 194-96 (Miller).

96. The only contemporaneous document in the record is a December, 1996, draft abstract prepared by Novo in Denmark for upcoming medical society meetings, and stating that the data from the Moses Study "suggest" that the claimed combination "*may* have synergistic properties in this type of patients." DX 9 (emphasis added); 6/7/10 Tr. at 84-85 (Moses); *see also* DX 12, PX 206, PX 207. Garber, who studied the paper trail, stated in response to a question by the Court that he did not recall anything exclusive of the trial record that described the results of the Moses Study as surprising and unexpected. 8/11/10 Tr. at 189-90 (Garber). As such, the Moses Study does not support Novo's contention that the claimed

combination produces unexpected results in Type II diabetes patients.

(ii) The Sturis Study

97. Novo also relies upon the Sturis Declaration, which was submitted to the examiner to reinforce the results of the Moses Study in demonstrating unexpected and synergistic results from the claimed combination therapy. Sturis stated in his Declaration that his test results showed ". . . synergistic effects on glucose tolerance in Zucker obese rats and that this data, taken together with the data presented in Example 3 of the present application, strongly suggests that the combination of repaglinide and metformin has synergistic properties in type 2 diabetic patients." JX 2A at Tab 14, C0173015, 10/16/2002.

98. Sturis used Zucker obese rats for his tests. These rats are an accepted animal model with excellent predictive capabilities for humans with Type II diabetes.[16] Sturis, however, admitted at trial that his test results may not translate to humans, and that was why he relied upon the Moses Study's results as well to support his conclusion of "strongly suggest[ed]" synergy in humans. 6//9/10 Tr. at 22-24, 88-89 (Sturis). Notably, the final draft of his abstract of his study stated that "[t]he presence of greater-than additive effects *may* be of relevance to the clinical efficacy of the claimed combination." PX 242 (emphasis added). Three days after his Declaration, Sturis' PowerPoint presentation to Novo's core group in charge of repaglinide development stated with re-

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[16] *See* ¶ 25, n.10, *supra*.

spect to the Moses Study that it was "not possible to assess whether REP/MET combination is additive, synergistic or antagonistic," by which he meant that it was not statistically possible to so assess. DX 56 at 105702; 6/9/10 Tr. at 91-93, 97 (Sturis). These two documents were not provided to the examiner. Sturis was unwilling to testify that the two studies together proved synergism in Type II patients. *Id.* at 99.

99. Caraco attacks several aspects of the Sturis Study, including the statistical analysis and his selection of a data point that departed from his test protocol. These issues are addressed below in Part VIII(A)(1)(a), dealing with the inequitable conduct issues.

100. The Sturis Study, while pertinent to the synergy debate, is not probative on the question of whether the claimed combination produces unexpected results in Type II diabetes patients.

(iii) The Pfeiffer Study

101. Novo also relies upon a 2003 Novo-funded study by Pfeiffer. The study compared the insulin sensitivity of patients taking only metformin with that of the same patients after they had taken the metformin/repaglinide combination. Because repaglinide is an insulin secretagogue and not an insulin sensitizer, Novo contends that one of ordinary skill in the art would not have expected the results observed by Pfeiffer: the insulin sensitivity of the patients taking both drugs was 35% greater than when those same patients were taking metformin alone. Pfeiffer Study, Pfeiffer II Study, 6/8/10 Tr. at 106-10 (Pfeiffer). Pfeiffer testified that the extent of this increase was extraordinary, statistically significant, clearly

synergistic and unexplainable even today. *Id.* at 102, 110, 118.

102. Accili questioned the reliability of conclusions that can be drawn from the Pfeiffer Study, based upon the small number of patients (eleven) and the wide range of their base line characteristics, such as body mass and changes in insulin sensitivity. 6/2/10 Tr. at 38 (Accili). *See also*, 8/11/10 Tr. at 151-52 (Garber). Caraco also asserts that Pfeiffer's results were fully predicted by the prior art Clark article, which taught that even monotherapy with an insulin secretagogue could increase insulin sensitivity. Clark at 9243; 6/8/10 Tr. at 144-49 (Pfeiffer). In response, Pfeiffer pointed out that Clark's study was with a very different type of patient. In contrast to Clark['s] patients, who were suffering from glucose toxicity, the Pfeiffer Study patients were well controlled on metformin. Pfeiffer testified that reduction in glucose toxicity could therefore not fully explain the 35% increase in sensitivity; it would only account for about a 10% increase in sensitivity. *Id.* at 144-46, 179-83 (Pfeiffer).

103. Pfeiffer's trial testimony is inconsistent with the explanation found in his contemporaneous report of his 2004 Study. There, he discussed two possible explanations for the improved insulin sensitivity. He admitted at trial that he copied his first explanation, almost verbatim, from the Clark article. 6/8/10 Tr. at 155-58 (Pfeiffer). The texts of Clark and of Pfeiffer are shown below (and in DX 416):

> The extrapancreatic effects – glucose metabolized per unit of insulin – of glimepiride treatment observed in this study are likely to

> be secondary to the improved glycemic control during the week of therapy. The latter would be associated with an increase in insulin mediated glucose disposal.

Clark at C0209243.

> This extrapancreatic effect may be related to the improved glycemic control during the one week of treatment hence to the reduction of hyperglycemia-induced insulin resistance (Yki-Jarvinen, 1992). The latter would be associated with an increase in insulin mediated glucose disposal.

Pfeiffer at NOVO-0005433.

104. This discussion describes the glucose toxicity issue, for which Pfeiffer cited Yki-Jarvinen but not Clark's article, which he admittedly copied. 6/8/10 Tr. at 155-58 (Pfeiffer); *see also*, 8/11/10 Tr. at 148-49 (Garber). Pfeiffer's report included "an alternative explanation" for which he cited prior art sources (including Clark), but he concluded that it was "*incredibly likely* that the improvement of insulin sensitivity is related to a waning of glucose toxicity." (Pfeiffer Study at NOVO-0005433, emphasis added).

105. Pfeiffer's contemporaneous explanation that he copied from Clark's prior art article (i.e., waning of glucose toxicity) for the increased insulin sensitivity found in his test results is entitled to greater credibility and weight than his trial testimony that those results were unexpected and unexplainable.

106. Aside from the issue of unexpected results, Pfeiffer's testimony concerning his study contradicts Novo's position that the study is evidence supporting

the nonobviousness of the claimed invention. Pfeiffer contended that his study's patient population was not suffering from glucose toxicity because they were well controlled on metformin at the time therapy with the metformin/repaglinide combination began. But Novo asserts that Claim 4 of the '358 Patent is explicitly limited to use for patients "in need of such treatment," i.e., in need of the combination therapy (Post-Trial Brief at 34, emphasis added). If Pfeiffer's patients were already well controlled, and therefore not "in need," then his test results cannot be probative of a "dramatic and unexpected effect of the [claimed] combination therapy" on those in need. *Id.* at 25. Thus, the Pfeiffer Study does not support a finding that the results of the combination was unexpected.

(iv) Scope of Claim 4

110. Also relevant to obviousness in terms of expected results is a determination as to the scope of Claim 4 of the '358 Patent, which specifies a method "for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need" [of] the claimed combination[.] As previously stated, the examiner ultimately granted Claim 4 "solely" on the basis of the Sturis Declaration concerning his rat study and "reconsideration of the synergistic effects demonstrated in Example 3, pages 11-12 of the specification, and Table I, page 14." JX 2A, Tab 17 at C0173146.

111. During discovery, Novo admitted that Claim 4 covers "all instances in which repaglinide is administered in combination with metformin to treat NIDDM." 6/8/10 Tr. at 84-85 (Novo Response to Request for Admission No. 203)[.] Now, Novo contends

that Claim 4 is limited to use for patients "*in need of such treatment*." Novo Post-Trial Br. at 34 (emphasis by Novo). Other than stating that it does not assert that the claimed combination therapy is needed by all Type II diabetes patients, Novo does not specify who is "in need of such treatment" or how to determine whether such need exists.

112. To the extent that there is a difference in scope between "all instances" of administration and administration only to those "in need," Novo should be bound by its earlier admission. Further, Novo would presumably assert that all administrations of the claimed combination would be an infringement, without inquiring into whether the patient really was "in need" of that particular treatment.

113. By Novo's admission, Claim 4 necessarily covers administration of the combination to, e.g., patients who are drug-naïve who start on the metformin/repaglinide combination without previously having taken any OADs. Drug-naïve patients are a known and quantifiable sub-population of NIDDM patients who have received the claimed combination therapy. *See* PX 175 at NOVO-6900704, 6900707 (showing monthly totals of drug-naïve patients starting on such combination therapy).[17]

114. Novo presented no evidence that the claimed combination therapy produced unexpected or syner-

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[17] PX 175 is a compilation of historical prescription data (including, e.g., prescriptions for repaglinide, metformin and the combination thereof) published by IMS, the industry standard source for pharmaceutical market data. 8/10/10 Tr. at 22 (Reisetter).

gistic results in drug-naïve patients. In fact, the evidence is to the contrary. In one Novo Integrated Clinical Trial Report where 56% of the tested patients were drug-naïve ("OHA-naïve" or oral antiglycemic agent-naïve, in that Report), "the synergistic effect of combination therapy observed by Moses et al was not consistently seen in this trial." (AGEE-3010, dated 12/2/02[,] at NOVO-0029328-29). In another, where all of the tested patients were drug-naïve, the conclusion was that "the combined therapy has not shown statistically better results than the drugs used in monotherapy." (AGEE-1411, dated 2/20/06, at NOVO-1008845 and 1008897).

115. The '358 Patent Abstract and the Field of the Invention both identify just one group: "NIDDM patients poorly controlled on metformin alone." The Moses Study was designed to compare the results of metformin/repaglinide combination therapy with monotherapy with either drug "in NIDDM patients inadequately controlled on MET alone." JX 1, at col. 7:66 to 8:3. The specification summarized the results by saying that: "the data also suggest that the combination of REP and MET may have synergistic properties in this type of patient." *Id.* at col. 8:30-31[.] Novo's other unexpected-result evidence was confined to Zucker obese rats (the Sturis Study) and patients whose glucose levels were adequately controlled on metformin (the Pfeiffer Study).[18]

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[18] It would appear that the latter group, being adequately controlled, were not "in need" of combination therapy. If, as Novo belatedly asserts, the scope of Claim 4 is confined to patients "in need," then the Pfeiffer Study cannot be evidence of

116. The type of NIDDM patient involved in the Moses Study (those failing on metformin alone) represents less than 25% of Type 2 diabetes patients. 8/11/10 Tr. at 127 (Garber). Müller admitted that the Moses Study results could not be extrapolated to other patient populations. 6/8/10 Tr. at 77. *See also*, 6/2/10 Tr. at 29 (Accili). Other Novo studies conducted on other patient sub-populations yielded results that were "inconsistent" with, and even "contrary to," those of the Moses Study. AGEE-3018 at 57; AGEE-3011 at 62, AGEE-1411 at 54. When Damsbo was asked how important the characteristics of a tested patient population is, he answered:

> You have to remember that Type II diabetes is a disease where you have different categories. People have different levels of the disease. So *it's very important* that the population you pick out for a starting is the same, meaning that they have the same weight, the same body mass index, the same glucose levels and the same – that the match each other. *That's critical*.

8/5/10 Tr. at 90-91 (emphasis added).

117. Consistent with Damsbo's testimony, Novo has argued that the Moses test results cannot properly be directly compared with those of the prior art DeFronzo and Hermann/Melander studies because of differences in the tested patient populations.

[Footnote continued from previous page]

unexpected results achieved by the claimed invention. Novo cannot have it both ways.

118. The Moses Study, and the evidence submitted to the Patent Office was limited to one type of patient (not counting the Zucker obese rats). Solely on the basis of that evidence, the examiner allowed Claim 4. Other patients might well have different results from the same treatment. 8/5/10 Tr. at 108 (Damsbo).

119. Thus, even if the Moses Study results in one narrow NIDDM patient sub-population were found to be unexpected, the record does not support a conclusion that the claimed combination would generate unexpected results in "all instances" of administration of that combination to NIDDM patients. In fact, the record is to the contrary, as exemplified by the evidence described above. Therefore, this is not a case where "one having ordinary skill in the art could ascertain a trend in the exemplified data which would allow him to reasonably extend the probative value thereof." *In re Clemens*, 622 F.2d 1029, 1036 (C.C.P.A. 1980). Novo could have, but did not seek a patent claim restricted in scope to patients failing on metformin alone, or even to those failing on insulin sensitizers generally.

120. Just as a broad independent claim cannot be unobvious when a narrower dependent claim is invalid as obvious, *see Comaper Corp. v. Antec. Inc.*, 596 F.3d 1343, 1350 (Fed. Cir. 2010), so here, when the evidence concerning a subset of Claim 4 (drug-naïve patients) showed no improvement over monotherapy, then prima facie obviousness of Claim 4 has not been overcome by Novo's evidence of alleged unexpected results confined to one narrow subset of patients.

(c) Commercial Success

121. Novo's claim of commercial success of the claimed invention is "a short horse soon curried."[19]

122. Only about 0.5% of NIDDM patient prescriptions for oral anti-diabetes drugs are for the claimed repaglinide/metformin combination. PX 262; 8/10/10 Tr. at 33, 35 (Reisetter). Further, from 2003 to 2007, the number of prescriptions for the claimed combination dropped from 1.24% to 0.71% of the total NIDDM patients taking OADs. PX 175; 8/10/10 Tr. at 41 (Reisetter). Reisetter, Novo's commercial success expert, agreed that use of the claimed combination dropped by 25% from 2003 to 2007. PX 366A; 8/10/10 Tr. at 44-45, 92-93.

123. As cited above, both Garber and Accili stated [a] preference for other combination therapies in their practice.

124. As evidence of commercial success or copying, Novo cites the fact that six major generic drug manufacturers have filed ANDAs for repaglinide. That argument has been rejected by the Federal Circuit. *See Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 377 Fed. Appx. 978, 2010 WL 2203101, at *4 (Fed. Cir. 2009) ("we do not find compelling Purdue's evidence of copying in the ANDA context where a showing of bioequivalency is required for FDA approval"). Here, the record shows that to the extent that Caraco and other generic manufacturers are seeking to market

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[19] According to the Oxford Dictionary of Proverbs, this centuries-old saying means "A slight task is soon completed. Curried here means 'groomed with a curry-comb.'"

the combination, they are doing so only under duress because of a belief that Novo had manipulated the FDA Orange Book. This conduct has prevented them from carving out the combination from their proposed labels for repaglinide, the patent on which has expired. Novo's expert on commercial success conceded that these activities of the generic manufacturers should not be characterized as evidence of commercial success of the claimed combination. 8/10/10 Tr. at 69 (Reisetter).

125. The record falls far short of establishing commercial success of the combination therapy of Claim 4.

B. Conclusion

126. Claim 4 of the '358 Patent is invalid because the claimed combination was obvious to a person of ordinary skill in the art at the time the invention was made. Whether measured against the teaching/suggestion/motivation test or the obvious-to-try test, the record contains an abundance of clear and convincing evidence establishing a strong prima facie case of obviousness.

127. That strong prima facie case of obviousness has not been overcome by Novo's attempt to prove unexpected results and commercial success. Clear and convincing evidence establishes that the results of the claimed combination therapy said by Novo to be unexpected and unexplainable were, to the contrary, expected and explainable in light of the state of the art as of the critical date. Further, the scope of Claim 4 substantially exceeds the scope of the evidence of allegedly unexpected results, and the record clearly and convincingly precludes extending the pro-

bative value of those results beyond the small Type II diabetes patient sub-population that experienced them. Finally, the record fails to establish that the claimed invention has been commercially successful.

VIII. INEQUITABLE CONDUCT

A. Discussion

1. Materiality

128. Caraco contends that material information concerning the Moses Study and Sturis Study was, with an intent to deceive the patent examiner, omitted and misrepresented by Sturis and Bork, the attorney who prosecuted the '358 Patent. Attention is primarily directed to their communications to the examiner on October 16, 2002. JX 2A at Tab 14.

129. As more fully quoted above (¶ 27, *supra*), the examiner's decision to allow Claim 4 of the '358 Patent was "[b]ased solely on the Sturis Declaration and reconsideration of the synergistic effects demonstrated in Example 3, pages 11-12 of the specification, and Table I, page 14." *Id.* at Tab 17, C0173146. In light of the examiner's previous four rejections based on obviousness, it is clear that the examiner considered the representations of Sturis and Bork concerning synergy (along with Example 3 of the specification) to be highly material to her decision on patentability.

130. The question of unexpectedness of results, rather than the fact or degree of synergism of those results, is the relevant inquiry as to whether prima facie obviousness has been overcome (*see* n[.]4, *supra*). It is not necessary to delve any deeper into the thicket of disputed evidence and arguments relating

to whether mathematical proof of synergism was established by either the Moses Study or Sturis Study. Nevertheless, representations to the Patent Office by Sturis and Bork about alleged synergism are relevant to the issue of inequitable conduct, in view of the examiner's focus on synergism as the sole basis for the allowance of Claim 4.

(a) The Sturis Declaration

131. Caraco asserts that the Sturis Declaration: (1) highlighted a statistically significant[20] test data point (the two-hour point) that, unknown to the examiner, was not part of his original test protocol; (2) failed to tell the examiner that the area under the glucose vs. time curve, which proved to be statistically insignificant, was the test protocol's primary endpoint; (3) failed to tell the examiner that the rat study alone did not establish that the claimed combination is synergistic in humans; (4) failed to tell the examiner that, as he reported to a Novo team responsible for repaglinide development, it was "*not possible* to assess whether rep/met combination additive, synergistic or antagonistic" based on the Moses Study, and that the Moses Study was not designed to show synergy. 6/9/10 Tr. at 74, 82-84, 130 (Sturis); DX 56 at NOVO-1015702 (emphasis added).

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[20] Statistical analyses that result in "p" values of 0.05 or less are, by accepted standards, considered statistically "significant," while values greater than 0.05 are not. 6/7/10 Tr. at 173-74 (Pagano). The p-value is a value that statisticians use to show the uncertainty in the results of a study. Values of 0.05 or less mean that there is 5 percent or less likelihood that the outcome is the result of pure chance. *Id.* at 126-27.

132. At the time of his Declaration, Sturis was a non-physician Principal Scientist at Novo Nordisk. Responding to the Court's questions, he testified that he knew that mathematical proof of synergy is helpful in getting a patent, and that the Patent Office is interested in knowing whether there is mathematical proof of synergy. 6/9/10 Tr. at 47 (Sturis). For him to be satisfied that there is synergy, he "needed statistical evidence." *Id.* at 49. Sturis knew that the Moses Study did not demonstrate synergy from a statistical point of view. *Id.* Before the filing of his Declaration, Sturis told Bork that the Moses Study did not demonstrate synergy with statistical proof, and that "you needed mathematical proof" to argue synergy to the Patent Office. *Id.* at 52; *see also*, *id.* at 42-43, 47, 53.

133. At trial, Sturis further acknowledged that viewing the Moses Study and his rat study together, he would not say that they "prove[d]" that the claimed combination has synergistic properties in human Type II diabetic patients. *Id.* at 99. Nevertheless, Sturis declared to the Patent Office that his rat study data showed:

> . . . synergistic effects on glucose tolerance in Zucker obese rats and that this data, taken together with the data presented in Example 3 of the present application, strongly suggests that the combination of repaglinide and metformin has synergistic properties in type 2 diabetic patients.

Id. at Tab 14, C0173015, 10/16/2002[.]

134. Accili testified that Sturis' use of the qualifier "suggests" was appropriate, and that he had no disagreement with this qualified statement. Pagano, a

biostatistics expert, acknowledged that the Sturis Declaration informed the examiner of the p-values for both the area-under-the-curve and the two-hour test results, and that the tests were performed on rats rather than humans. 6/7/10 Tr. at 150-51.

135. However, Pagano criticized the fact that the two-hour data point, though statistically significant, was post hoc and "cherry-picked," in that it was not part of the original test protocol. Pagano explained that biostatisticians base their analyses on an established protocol, to avoid result-oriented conclusions. Calculation of p-values based upon a single data point that was not part of the original protocol should include a correction factor. However, Sturis did not do so with regard to the 0.02 p-value that he obtained for the two-hour test point. *Id.* at 128-32, 172-73 (Pagano).[21] Nor did Sturis inform the examiner that such data point was post hoc, or in the alternative submit the protocol so that the examiner could determine that on her own. *Id.* at 177 (Pagano); 6/9/10 Tr. at 83-84 (Sturis). Therefore, Pagano considered it "statistically unsound" for Sturis to conclude, as he expressly did with respect to that test point, that the p-value of 0.02 "shows that significant synergy exists" at that data point for the combination therapy.

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[21] Thaler testified that there is a "strict set of well-accepted guidelines for correcting or adjusting analysis obtained from the 'post hoc' analysis." 6/10/10 Tr. at 49-50 (Thaler). The Bonferroni correction is a method used in statistics to address the problems of multiple comparisons performed simultaneously. http://wikipedia.org/wiki/Bonferroni_correction (last visited Jan. 18, 2011).

JX 2A at Tab 14 at C0173015, ¶ 6B; 6/7/10 Tr. at 130-32.

136. Second, Pagano considered as incorrect Sturis' statement that the p-value of 0.061 for the protocol's original end-point of the area-under-the-curve "indicates a synergistic effect," because that p-value is greater than the 0.05 standard. *Id.* at 176-77. JX 2A, Tab 14 at C0173014, ¶ 6A. That assertion of "synergistic effect" is also contrary to Sturis' own standards requiring statistical proof. Sturis admitted that he did not disclose to the examiner that this data point was not statistically significant or that it was the protocol's primary endpoint. 6/9/10 Tr. at 63-65, 82 (Sturis).

137. Because Sturis himself admitted that the Moses Study did not prove synergism, and his rat study did not prove synergism in rats, Pagano found "no statistical support" for Sturis' stated conclusion that the combined rat and Moses Study "strongly suggests that the combination of repaglinide and metformin has synergistic properties in type 2 diabetic patients." 6/7/10 Tr. at 130-31.

138. Thaler's testimony that the Moses Study "support[s] the finding that a synergism exists between repaglinide and metformin," and that the Sturis Study "demonstrates that repaglinide and metformin have a synergistic effect," 6/10/10 Tr. at 36, is weakened by his acknowledgment that what he was saying was "[no]thing more than that the effect of the combination of the drugs that were used was greater than the sum of the effects of the individual drugs when given alone." *Id.* at 97.

139. Sturis did not represent to the examiner that synergism in humans was mathematically proven. He also knew that his "strongly suggests" statement could make the difference between Novo getting or not getting the patent. 6/9/10 Tr. at 85-86 (Sturis). His "strongly suggests" qualified conclusion concerning the combined effect of the two studies was aggressive advocacy. However, it must be said that it has not been shown by clear and convincing evidence to be false. Nonetheless, to the extent that the examiner drew further conclusions from the Sturis Declaration per se, they were not warranted.

140. Rather, it was the material omissions from the Sturis Declaration that violated his duty to disclose material information, not the representations. Undisclosed to the examiner were the facts that the two-hour data point was not part of the test protocol, and that a correction factor had not been applied to that p-value. That data point was the only one in his rat test that appeared to produce a statistically significant p-value of less than 0.05. Also undisclosed were Sturis' opinions (listed below) that, by his own standards requiring mathematical proof, neither his rat study nor the Moses Study alone proved synergy in humans.

141. Clearly, the examiner, focused as she was on the Sturis Declaration and the "synergistic effects" described in the patent specification, would have wanted to consider Sturis' expressed negative views on synergism, inconsistent as they were with the conclusions expressed or "strongly suggest[ed]" in his Declaration, and with Bork's exaggerated arguments

based on Sturis' view. Undisclosed to the examiner were Sturis' conclusions that:

> (1) the Moses Study "*did not demonstrate synergy*" with statistical proof. 6/9/10 Tr. at 42-43, 53, 129-30 (Sturis) (emphasis added). He expressed this opinion to Bork a few months before his Declaration to the Patent Office;
>
> (2) it is "*not possible* [based on Moses' Study] to assess whether rep/met combination is additive, synergistic or antagonistic." DX 56 at NOVO-0105702 (emphasis added); 6/9/10 Tr. at 130 (Sturis). He expressed this conclusion to the Novo core repaglinide development group just a few days after his Declaration;
>
> (3) his rat study was not designed to test for synergy in humans, and the results "do not necessarily translate into humans;" 6/9/10 Tr. at 74. Indeed, in the abstract of his rat study report he was only willing to state that "[t]he presence of greater-than-additive effects may be of relevance to the clinical efficacy of the REP-MET combination." DX 74; PX 242[;] *id*. at 77.
>
> (4) his rat study alone does not prove that the claimed combination is actually synergistic in humans. *Id.*
>
> (5) even viewing the Moses Study and Sturis study together, Sturis would not say that they "prove[d]" that the claimed combination

> has synergistic properties in human Type II diabetic patients. *Id.* at 99.

142. Clear and convincing evidence is present that the opinions of Sturis were highly material to the patentability of Claim 4, because they refuted or were inconsistent with the opinions expressed in his Declaration in support of patentability. 37 C.F.R. § 1.56(b)(2). A reasonable examiner, focused on the issue of synergism as was the examiner here, would have wanted to consider any qualifications or reservations held by Sturis concerning the conclusions he expressed in his Declaration.

> The fact that the conduct here consists of an omission rather than a *misrepresentation* does not compel a different result, as either may mislead an examiner. An examiner must be able to evaluate information in an affidavit in context, giving it proper weight . . . Affidavits are inherently material, even if only cumulative. The affirmative act of submitting an affidavit must be construed as being intended to be relied upon.

Refac Intern., Ltd. v. Lotus Development Corp., 81 F.3d 1576, 1582-83 (Fed. Cir. 1996) (emphasis in original). Indeed, the examiner's explicit reliance on the Sturis Declaration warrants the conclusion that the Declaration satisfied the alternative "but for" materiality test. *Digital Control*, 437 F.3d at 1315-16.

(b) The Bork Representations

143. In support of the Sturis Declaration, Bork asserted in response to the Final Rejection:

> Applicant therefore submits that the data presented in the application, in combination with the data presented in the Declaration of Dr. Sturis, provides *clear evidence of synergy* for the use of the claimed combination of repaglinide and metformin in the treatment of type II diabetes.
>
> . . . a prima facie case [of obviousness] is rebutted by the evidence of *synergistic and surprising results* achieved by the claimed combination therapy in humans (Example application) and in Zucker obese rats (Sturis' Declaration).

JX 2A, Tab 14 at C0173010 (emphasis added).[22]

144. In light of what Bork then knew, his representations to the examiner go beyond aggressive advocacy; the representations were known by him to be unsupported by the Sturis Declaration, and known to be untrue. With respect to synergistic results in humans, the Sturis Declaration never went beyond "strongly suggests." More importantly, Sturis had previously told Bork directly that the Moses Study

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[22] The patent specification states that, with respect to NIDDM patients, "[I]t has been found that there is a synergism between repaglinide and metformin." JX-1 at col. 3, lines 11-12[.] Sturis testified that such statement was talking about humans, not rats, and that he has seen no evidence proving synergism with the combination in humans. 6/9/10 Tr. at 128 (Sturis).

did not mathematically or statistically demonstrate synergy in humans. 6/9/10 Tr. at 53-54 (Sturis). Bork's representations, however, asserted "clear evidence of synergy" and "synergistic and surprising results" in humans[.] There is no evidence that Bork's exaggerations were based on any sources other than the Sturis Study and the Moses Study.

145. In addition to the contrary information possessed by Bork at the time of his representations to the examiner, he later received explicit contrary information from Sturis. On January 1, 2003 (the '358 Patent issued a year later, on January 13, 2004), Sturis sent an e-mail to Bork, enclosing a final draft of the repaglinide/metformin abstract. The abstract sent to Bork stated: "The presence of greater-than-additive effects *may* be of relevance to the clinical efficacy of the REP-MET combination." DX 74; PX 242; 6/9/10 Tr. at 77 (Sturis) (emphasis added). Bork's duty to disclose this highly qualified statement, inconsistent with his own earlier representations to the examiner, continued until the issuance of the patent, over one year later:

> The duty to disclose information exists with respect to each pending claim until the claim is cancelled or withdrawn from consideration, or the application becomes abandoned.

37 C.F.R. § 1.56(a).

146. The evidence is clear and convincing that Bork's representations of October 16, 2002, as well as his failure to correct them in light of the later-received information described above, went beyond acceptable advocacy because they did not contain the limitations and qualifications communicated to him

by Sturis. Further, they were highly material to patentability, because their absolute and unqualified character "refutes, or is inconsistent with, a position the applicant takes in . . . asserting an argument of patentability." *Id.* at § 1.56(b)(2). As in the case of the Sturis Declaration, they also satisfy the alternative "but for" materiality test. *Digital Control*, 437 F.3d at 1315-16.

(c) Novo's Post-Clinical Trials

147. Caraco also relies upon Novo's failure to disclose to the Patent Office the unfavorable results of several clinical trials of the repaglinide/metformin combination Novo conducted while the application for the '358 Patent was pending. In two of the trials that had been completed before the patent issued, "the synergistic effect of combination therapy observed by Moses et al was not consistently seen" (AGEE-3018 at 57; AGEE-3018 at 62). The former study concluded that "[t]he results observed in this study were *contrary* to the study by Moses et al." AGEE-3018 at 57 (emphasis added).

148. Although Müller was Novo's lead scientist in connection with repaglinide's development, and these studies were conducted out of Novo's New Jersey facility during his tenure there, he was "surprised" that he knew nothing of them until this litigation. 6/8/10 Tr. at 53 (Müller). There is no contradictory evidence concerning his unawareness of these test results in the record. And there is no evidence that Novo informed Bork of the existence or content of these test results.

149. These two Novo post-clinical trials were highly material to patentability because they refuted

or were inconsistent with Novo's representations to the Patent Office concerning the synergistic results of the Moses Study. 37 C.F.R. § 1.56(b)(2).

150. Admittedly, there is no evidence that Müller, Sturis or Bork were aware of these test results, or that Novo deliberately concealed that information from them. Under the applicable Patent Office Rules, those were the only three Novo individuals to whom the duty of candor and disclosure applied, there being no record of any other inventors, attorneys or other persons substantively involved in the preparation or prosecution of the patent application. *Id.* at § 1.56(c). *Compare, Synthon IP, Inc. v. Pfizer, Inc.*, 472 F. Supp. 2d 760, 779-80 (E.D. Va. 2007), *aff'd per curiam on inequitable conduct*[,] [281 Fed. Appx. 995] (Fed. Cir. 2008) (non-precedential):

> [T]he duty of candor cannot be avoided by willful ignorance or compartmentalization of knowledge within a company in an effort to insulate the patent applicants and their attorneys from information unfavorable to patentability.

See also, Ranbaxy Laboratories Ltd. v. Abbott laboratories, 2005 U.S. Dist. LEXIS 27753, 2005 WL 30503608, at *8 (N.D. Ill. Nov. 10, 2005). Further, the bare fact that undisclosed material information existed within a patent assignee company is insufficient to impose an obligation of disclosure. *Nordberg, Inc. v. Telsmith, Inc.*, 82 F.3d 394, 397 (Fed. Cir. 1996).

151. Overall, it must be said that Caraco did not establish by clear and convincing evidence that there was any inequitable conduct relating to Novo's fail-

ure to disclose these post-clinical trials to the Patent Office.

2. Intent

152. Sturis, as discussed above, withheld from the Patent Office the opinions he expressed to Bork and to Novo's core repaglinide development group concerning the individual significance of each of the Moses Study and his own study. Sturis also withheld his opinion, expressed at trial, that synergistic properties in humans were not proven even when these two study results are viewed together. Before the filing of his Declaration, Sturis was already aware that a showing of synergy was helpful in securing a patent, and that the examiner would be interested in knowing if there were mathematical proof of synergy. DX 79; 6/9/10 Tr. at 43-47, 85-86 (Sturis).

153. There is clear and convincing evidence in the record justifying the inference that Sturis had the intent to deceive the Patent Office by withholding his opinions and conclusions respecting the significance of the results of the Moses Study and the Sturis Study. He knew of the importance of synergism to the examiner's consideration of the patentability of the claimed invention. The close relationship of his withheld opinions and conclusions to those in his Declaration was inescapable. No plausible reason for his omissions, other than an intent to deceive, has been offered. Under the circumstances, no other reason would be credible. *McKesson, supra*, 487 F.3d at 913; *Praxair, supra*, 543 F.3d at 1313-14. An intent to deceive is the "single most reasonable inference able to be drawn from the evidence." *Star Scientific, supra*, 537 F.3d at 1365.

154. As previously stated, Bork was fully informed by Sturis himself of the qualified and contrary opinions he held. Bork's exaggerated arguments to the examiner in support of the Sturis Declaration went beyond aggressive advocacy; they misstated key conclusions. As a patent attorney, he had to have known of the materiality of his representations and the significance attached to them by the examiner. As in the case of Sturis, no plausible explanation, other than an intent to deceive, was offered, and none would be reasonable or credible under the circumstances. It is important to note that although Novo brought to trial witnesses from across this country and several from Europe and Australia, it did not bring Bork (presumably still in New Jersey) to testify concerning his role in the prosecution of the patent application.

155. Additional evidence of Novo's less than rigorous attitude toward its duty of candor arises from its untimely filing of the Ajinomoto Opposition papers that were filed against Novo's corresponding European application. That opposition, filed in February, 2002, presented prior art based arguments against the patentability of the European application. Novo filed its response in the European Patent Office in February, 200[2]. JX 2A at Tab 22, C0173163, item 4. It did not disclose the papers to the examiner until May 6, 2003. *Id.* at C0173162, items 1 and 4 and attached Form PTO-1449 at C0173167. Novo's submission to the Patent Office did not occur until 15 months after the filing of the European Opposition, and four months after the Patent Office had allowed Claim 4 (application claim 29).

156. Applicable Patent Office rules require that an information disclosure statement (IDS), if not filed

within three months of the application's filing date or before the mailing of a first Office action, will still be considered if accompanied by a statement that the disclosed item "was first cited in a communication from a foreign patent office in a counterpart application not more than three months prior to the filing of the [IDS]," or that "to the knowledge of the person signing the certification after making reasonable inquiry," no person subject to the duty of disclosure was aware of such item more than three months prior to the filing of the IDS. 37 C.F.R. §§ (d) and (e). Bork failed to file the required statement, and Novo failed to provide the Court with any explanation for its long delay in filing the opposition evidence until after the examiner had allowed Claim 4.

157. The MPEP makes several references to the importance of timely filing of material information. Section 609 states that the relevant rules "are designed to encourage individuals to submit information to the Office *promptly*" (emphasis added). Section 2001.06(a) focuses on the duty to disclose material information from "related foreign applications." Suggestion No. 12 of Section 2004's list of "Aids to Compliance with Duty of Disclosure" advises that "potentially material information discovered late in the prosecution should be *immediately* submitted." (emphasis added).

158. Based upon Sturis' omissions of clearly material information, the similar omissions and misrepresentations by Bork, and the unexplained and therefore apparently calculated delay in filing the Ajinomoto opposition papers, an inference of intent to deceive the examiner is appropriately inferred. *Praxair, supra*, 543 F.3d 1306, 1313-14.

159. It is clear, however, that the finding of materiality is not the basis for finding intent. Indeed, the Federal Circuit has recently emphasized that

> . . . materiality and intent are separate requirements, and intent to deceive cannot be found based on materiality alone. *Larson Mfg. Co. of S.D., Inc. v. Aluminart Prods. Ltd.*, 559 F.3d 1317, 1340 (Fed. Cir. 2009). A court cannot simply infer that an applicant "should have known" the materiality of withheld information and thus intended to deceive the PTO because the applicant knew of the information and the information is material. A district court must find some other evidence that indicates that the applicant appreciated the information's materiality.

Cancer Research Technology Ltd. v. Barr Laboratories, Inc., 625 F.3d 724, 733-34 (Fed. Cir. 2010). As explained above, there is more than just the fact that the materials withheld from the Patent Office were material which establishes intent.

B. Conclusion

159. Under prevailing law, the evidence compels the conclusion that the '358 Patent is unenforceable due to inequitable conduct in the prosecution of the patent application before the Patent Office. Sturis withheld from his Declaration highly material information with intent to deceive the patent examiner. Bork both misrepresented and withheld highly material information with intent to deceive the examiner. The violations of the duties of disclosure by both men exceeds the necessary threshold levels of materiality

and intent, and the equities warrant the conclusion that inequitable conduct occurred, and therefore the '358 patent is unenforceable.

IX. CONCLUSION

A.

Based on the findings of fact and the governing law as above, Claim 4 of the '358 patent is invalid. The claimed combination of metformin with repaglinide was obvious to a person of ordinary skill in the art at the time of the invention. Whether measured against the teaching/suggestion/motivation test or the obvious to try test, the record of the trial contains clear and convincing evidence establishing a prima facie case of obviousness. The prima facie case of obviousness was not overcome by proof of unexpected results and commercial success. The results of the combination claimed to be unexpected and unexplainable were, to the contrary, to be expected and were explainable in light of the state of the art as of the critical date. The scope of Claim 4 substantially exceeds the scope of the evidence of the asserted unexpected results, and the record clearly and convincingly precludes extending the probative value of the results beyond the small Type II diabetes patient sub-population that experienced them. Finally, the evidence in the record did not establish that the claimed invention has been commercially successful.

B.

Also, based on the findings of fact and the governing law above, Claim 4 of the '358 patent is unenforceable because of inequitable conduct in its prosecution. Sturis withheld from his Declaration highly material evidence which misled the patent examiner.

Bork misrepresented and withheld highly material information from the patent examiner. The conclusion to be drawn from what Sturis and Bork did and did not do is that, with deceptive intent, they were successful in misleading the patent examiner to approve the application, which resulted in the issuance of the '358 patent.

C.

The Court is mindful of the attendant consequences of this decision. While Novo argued vigorously to sustain the '358 patent, at the end of the day the record simply does not support its arguments. Rather, the record shows, quite clearly, that the patent should never have issued. The idea to combine repaglinide with metformin was natural. Moreover, the results of the combination were not at all unexpected.

Novo knew the obstacles to obtaining a patent, as seen by the several rejections. Knowing what was needed to be shown to establish patentability, in what would be Novo's final attempt before the Patent Office, Novo omitted material information. The only inference which can be drawn from its conduct was that it was done with the intent to deceive the examiner and obtain a patent.

Perhaps market forces drove Novo to do what it did; the Court can only speculate. In the end, however, the patent cannot be sustained. An appropriate judgment will enter.

Dated: January 19, 2011

/s/ Avern Cohn

AVERN COHN

UNITED STATES DISTRICT JUDGE

JUDGMENT

For the reasons stated in the Decision entered this date,

IT IS ORDERED AND ADJUDGED that judgment be entered in favor of CARACO PHARMACEUTICAL LABORATORIES, LTD. and against NOVO NORDISK A/S and NOVO NORDISK, INC. as the Court finds that *U.S. Patent No. 6,677,358*B1, NIDDM REGIMEN is (1) not invalid because of anticipation, (2) invalid because of obviousness, and (3) not enforceable because of inequitable conduct.

Dated: January 19, 2011

/s/ Avern Cohn

AVERN COHN

UNITED STATES DISTRICT JUDGE

Appendix I
Reports and Articles Referenced in Decision

DX 52 – AGEE-3018 Integrated Clinical Trial Report, "Repaglinide A 3-month, open-label, randomized multi-center study of repaglinide in combination with metformin as compared to metformin or repaglinide given as monotherapy for the treatment of type 2-diabetes" (9/29/2003) ("AGEE-3018").

DX 53 – AGEE-3010 Integrated Clinical Trial Report, "NovoNorm A 16-week, multi-centre, open-labeled study on type 2 diabetic patients treated with repaglinide and repaglinide in combination with metformin" (12/2/2003) ("AGEE-3010").

DX 54 – AGEE-1411 Integrated Clinical Trial Report, "Multicentre, randomized, comparative, open, three armed parallel group study on the use of metformin, repaglinide or the combination of both in type 2 diabetic patients after failure of dietary measures" (2/20/06) ("AGEE-1411").

DX 61 – DeFronzo et al, "Efficacy of Metformin in Patients with Non-Insulin-Dependent Diabetes Mellitus," N. Engl. J. Med. (1995) ("DeFronzo").

DX 200 – Rachman et al, "Drugs on the Horizon for Treatment of Type 2 Diabetes," Diabetic Medicine (1995) ("Rachman").

DX 202 – The American Diabetes Association, "Consensus Statement: The Pharmacological Treatment of Hyperglycemia in NIDDM," Diabetes Care (1995) ("Consensus Statement").

DX 203 – Melander, "Oral Antidiabetic Drugs: an Overview," Diabetic Medicine (1996) ("Melander").

DX 212 – Kaku et al, "Possibility of the Appearance of New Antidiabetic Agents (1): Oral Antidiabetic Agents," Practice (1996) ("Kaku").

DX 246 – Hermann and Melander, "Therapeutic Comparison of Metformin and Sulfonylurea, Alone and in Various Combinations, A Double-Blind Controlled Study," Diabetes Care (1994) ("Hermann/Melander")

DX 307 – Karlsson and Garber, "Metformin Comes to America: What to Do Now," Clinical Diabetes (1995) ("Karlsson/Garber").

DX 311 – Clarke et al, "Combined Metformin-Chlorpropamide Therapy in 108 Diabetic Sulphonylurea Failures," The Lancet (1965) ("Clarke").

DX 319 – Rudovich, Pfeiffer et al, "Enhancement of Early- and Late-Phase Insulin Secretion and Insulin Sensitivity by the Combination of Repaglinide and Metformin in Type 2 Diabetes Mellitus," Exp. Clin. Endocrinal Diabetes, Vol. 112, No. 7, pp. 395-400 (2004) ("Pfeiffer Study").

DX 350 – Garber, "Incremental Therapy for NIDDM," Clinical Diabetes (1995) ("Garber I").

DX 351 – Garber, "Metformin Therapy for Type II Diabetes Mellitus," P&T (1995) ("Garber II").

DX 361 – Bristol-Myers Squibb Product Monograph, "Glucophage, Metformin Hydrochloride Tablets" (1995) ("Bristol-Myers").

DX 369 – Raskin, "Oral combination therapy: repaglinide plus metformin for treatment of type 2 diabetes," Diabetes, Obesity and Metabolism, 10:1167-77 (2008) ("Raskin").

DX 383 – Clark et al, "The Effect of Glimepiride on Pancreatic-Cell Function Under Hyperglycaemic Clamp and Hyperinsulinaemic, Euglycaemic Clamp Conditions in Non-Insulin-Dependent Diabetes Mellitus," Horm. Metab. Res. (1996) ("Clark").

PX 138 – Rudovich, Pfeiffer et al, "Enhancement of Early and Late Phase Insulin Secretion and Insulin Sensitivity by the Combination of Repaglinide and Metformin in Type 2 Diabetes Mellitus," Exp. Clin. Endocrinal Diabetes, Vol. 112, No. 7, pp. 395-400 (2004) ("Pfeiffer Study").

PX 201 – AGEE-053 Integrated Clinical Trial ("Moses Study" or "Australian Study").

PX 401 – Sturis et al, "Combination of repaglinide and metformin results in greater than additive (synergistic) effects on glucose tolerance in obese Zucker (fa/fa) rats" ("Sturis Study").

PX 438 – Roudavitch et al, "Repaglinide plus Metformin: effects on insulin secretion and sensitivity in type 2 diabetes" ("Pfeiffer II Study").

APPENDIX II

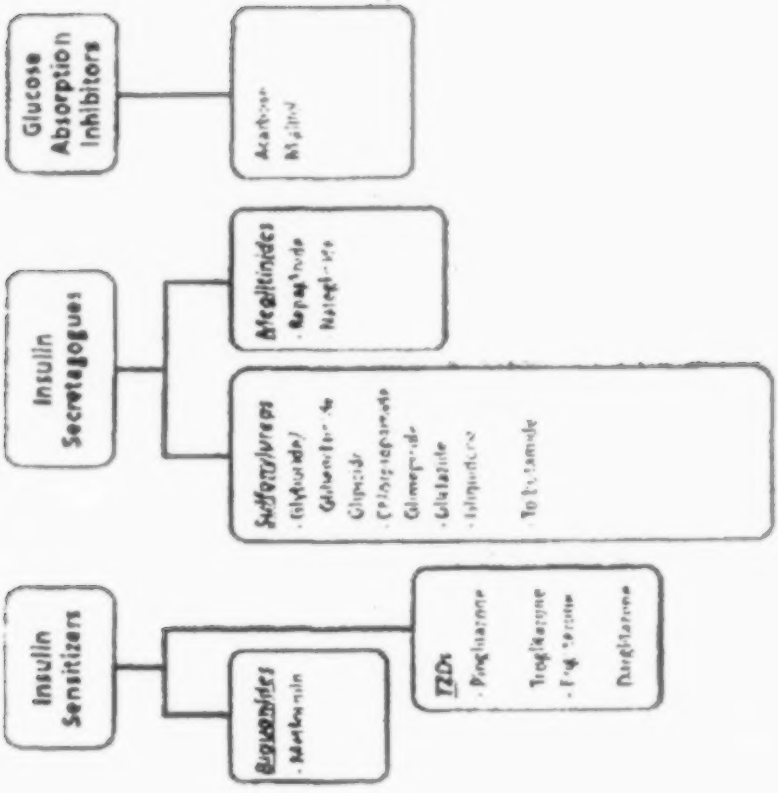
05-40188

Novo Nordisk A/S, et al

v.

Caraco Pharmaceutical, et al

APPENDIX II
05-40188
Novo Nordisk A/S, et al
v
Caraco Pharmaceutical, et al



APPENDIX C

35 U.S.C. § 271 provides:

§ 271. Infringement of patent

(a) Except as otherwise provided in this title [35 U.S.C. §§ 1 et seq.], whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent.

(b) Whoever actively induces infringement of a patent shall be liable as an infringer.

(c) Whoever offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.

(d) No patent owner otherwise entitled to relief for infringement or contributory infringement of a patent shall be denied relief or deemed guilty of misuse or illegal extension of the patent right by reason of his having done one or more of the following: (1) derived revenue from acts which if performed by another without his consent would constitute contributory infringement of the patent; (2) licensed or authorized another to perform acts which if performed

without his consent would constitute contributory infringement of the patent; (3) sought to enforce his patent rights against infringement or contributory infringement; (4) refused to license or use any rights to the patent; or (5) conditioned the license of any rights to the patent or the sale of the patented product on the acquisition of a license to rights in another patent or purchase of a separate product, unless, in view of the circumstances, the patent owner has market power in the relevant market for the patent or patented product on which the license or sale is conditioned.

(e) (1) It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

(2) It shall be an act of infringement to submit–

(A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. § 355(j)] or described in section 505(b)(2) of such Act [21 U.S.C. § 355(b)(2)] for a drug claimed in a patent or the use of which is claimed in a patent,

(B) an application under section 512 of such Act [21 U.S.C. § 360b] or under the Act of March 4, 1913 (21 U.S.C. [§§] 151-158) for a drug or veterinary biological product which is not primarily manufactured using recombinant DNA, recombinant RNA,

hybridoma technology, or other processes involving site specific genetic manipulation techniques and which is claimed in a patent or the use of which is claimed in a patent, or

(C) (i) with respect to a patent that is identified in the list of patents described in section 351(l)(3) of the Public Health Service Act [42 U.S.C. § 262(l)(3)] (including as provided under section 351(l)(7) of such Act [42 U.S.C. § 262(l)(7)]), an application seeking approval of a biological product, or

(ii) if the applicant for the application fails to provide the application and information required under section 351(l)(2)(A) of such Act [42 U.S.C. § 262(l)(2)(A)], an application seeking approval of a biological product for a patent that could be identified pursuant to section 351(l)(3)(A)(i) of such Act [42 U.S.C. § 262(l)(3)(A)(i)], if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug, veterinary biological product, or biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

(3) In any action for patent infringement brought under this section, no injunctive or other relief may be granted which would prohibit the making, using, offering to sell, or selling within the United States or importing into the United States of a patented invention under paragraph (1).

(4) For an act of infringement described in paragraph (2)–

(A) the court shall order the effective date of any approval of the drug or veterinary biological product involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed,

(B) injunctive relief may be granted against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug, veterinary biological product, or biological product,

(C) damages or other monetary relief may be awarded against an infringer only if there has been commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug, veterinary biological product, or biological product, and

(D) the court shall order a permanent injunction prohibiting any infringement of the patent by the biological product involved in the infringement until a date which is not earlier than the date of the expiration of the patent that has been infringed under paragraph (2)(C), provided the patent is the subject of a final court decision, as defined in section 351(k)(6) of the Public Health Service Act [42 U.S.C. § 262(k)(6)], in an action for infringement of the patent under section 351(l)(6) of such Act [42 U.S.C. § 262(l)(6)], and the biological product has not yet been approved because of section 351(k)(7) of such Act [42 U.S.C. § 262(k)(7)].

The remedies prescribed by subparagraphs (A), (B), (C), and (D) are the only remedies which may be granted by a court for an act of infringement described in paragraph (2), except that a court may award attorney fees under section 285 [35 U.S.C. § 285].

(5) Where a person has filed an application described in paragraph (2) that includes a certification under subsection (b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. [§] 355), and neither the owner of the patent that is the subject of the certification nor the

holder of the approved application under subsection (b) of such section for the drug that is claimed by the patent or a use of which is claimed by the patent brought an action for infringement of such patent before the expiration of 45 days after the date on which the notice given under subsection (b)(3) or (j)(2)(B) of such section was received, the courts of the United States shall, to the extent consistent with the Constitution, have subject matter jurisdiction in any action brought by such person under section 2201 of title 28 for a declaratory judgment that such patent is invalid or not infringed.

(6) (A) Subparagraph (B) applies, in lieu of paragraph (4), in the case of a patent–

(i) that is identified, as applicable, in the list of patents described in section 351(l)(4) of the Public Health Service Act [42 U.S.C. § 262(l)(4)] or the lists of patents described in section 351(l)(5)(B) of such Act [42 U.S.C. § 262(l)(5)(B)] with respect to a biological product; and

(ii) for which an action for infringement of the patent with respect to the biological product–

(I) was brought after the expiration of the 30-day period described in subparagraph (A) or (B), as applicable, of section 351(l)(6) of such Act [42 U.S.C. § 262(l)(6)]; or

(II) was brought before the expiration of the 30-day period described in subclause (I), but which was dismissed without prejudice or was not prosecuted to judgment in good faith.

(B) In an action for infringement of a patent described in subparagraph (A), the sole and exclusive remedy that may be granted by a court, upon a finding that the making, using, offering to sell, selling, or importation into the United States of the biological

product that is the subject of the action infringed the patent, shall be a reasonable royalty.

(C) The owner of a patent that should have been included in the list described in section 351(l)(3)(A) of the Public Health Service Act [42 U.S.C. § 262(l)(3)(A)], including as provided under section 351(l)(7) of such Act [42 U.S.C. § 262(l)(7)] for a biological product, but was not timely included in such list, may not bring an action under this section for infringement of the patent with respect to the biological product.

(f) (1) Whoever without authority supplies or causes to be supplied in or from the United States all or a substantial portion of the components of a patented invention, where such components are uncombined in whole or in part, in such manner as to actively induce the combination of such components outside of the United States in a manner that would infringe the patent if such combination occurred within the United States, shall be liable as an infringer.

(2) Whoever without authority supplies or causes to be supplied in or from the United States any component of a patented invention that is especially made or especially adapted for use in the invention and not a staple article or commodity of commerce suitable for substantial noninfringing use, where such component is uncombined in whole or in part, knowing that such component is so made or adapted and intending that such component will be combined outside of the United States in a manner that would infringe the patent if such combination occurred within the United States, shall be liable as an infringer.

(g) Whoever without authority imports into the United States or offers to sell, sells, or uses within the United States a product which is made by a proc-

ess patented in the United States shall be liable as an infringer, if the importation, offer to sell, sale, or use of the product occurs during the term of such process patent. In an action for infringement of a process patent, no remedy may be granted for infringement on account of the noncommercial use or retail sale of a product unless there is no adequate remedy under this title for infringement on account of the importation or other use, offer to sell, or sale of that product. A product which is made by a patented process will, for purposes of this title, not be considered to be so made after–

(1) it is materially changed by subsequent processes; or

(2) it becomes a trivial and nonessential component of another product.

(h) As used in this section, the term "whoever" includes any State, any instrumentality of a State, and any officer or employee of a State or instrumentality of a State acting in his official capacity. Any State, and any such instrumentality, officer, or employee, shall be subject to the provisions of this title in the same manner and to the same extent as any nongovernmental entity.

(i) As used in this section, an "offer for sale" or an "offer to sell" by a person other than the patentee, or any designee of the patentee, is that in which the sale will occur before the expiration of the term of the patent.

REPLY BRIEF

Supreme Court, U.S.
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MAR 7 - 2011
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No. 10-844

In the Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD. AND SUN PHARMACEUTICAL INDUSTRIES, LTD., PETITIONERS

v.

NOVO NORDISK A/S AND NOVO NORDISK, INC., RESPONDENTS

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

REPLY TO BRIEF IN OPPOSITION

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PARTIES TO THE PROCEEDINGS

The Rule 29.6 Statement included in the petition for a writ of certiorari, as updated by the brief in opposition for respondents, remains accurate.

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REPLY TO BRIEF IN OPPOSITION

Respondents' brief in opposition does not diminish our showing that the ruling below raises vital issues warranting immediate review. Respondents concede that they are using their patent to block Caraco from marketing drugs that do not infringe. And as confirmed by five *amicus* briefs—representing millions of consumers, generic and branded manufacturers, and the leading trade association—the Federal Circuit's splintered ruling enabling this easy-to-replicate tactic threatens not only settled intellectual property rights in a $300 billion industry, but the interests of consumers and the FDA's ability to administer Hatch-Waxman.

The Court need not take our word for it, however. After the Federal Circuit sanctioned respondents' use code abuse, their own counsel hailed the ruling as an "important decision construing the Hatch-Waxman counterclaim and section viii carve-outs"—a "groundbreaking case" that promises to "benefit innovator drug companies facing Hatch-Waxman counterclaims," "especially * * * in the method of use context, where the FDA looks to use codes provided by NDA holders * * * in evaluating requests by ANDA applicants for section viii carve-outs."[1] Read: Name-brand drug makers now have unchecked power to circumvent Section viii by submitting overbroad use codes.

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[1] Mark A. Perry, *Federal Circuit Issues Important Decision Construing the Hatch-Waxman Counterclaim and Section viii Carve-Outs*, available at: http://www.gibsondunn.com/publications/pages/FederalCircuitDecisionConstruingHatchWaxmanCounterclaim.aspx.

Now, however, respondents say "the counterclaim has *nothing to do* with section viii carve-outs" and "there is nothing to suggest that [the question presented] will arise again." Opp. 13. But as their out-of-court statements confirm, the issue here is important, recurring, and integrally related to the FDA's administration of Section viii.

Indeed, as the D.C. Circuit has recognized, the counterclaim is pivotal to Hatch-Waxman's "incentive structure" (Pet. 27-29), and use codes have doubled since 2003 (Pet. 23). Moreover, the problem is certain to worsen now that brands have the go-ahead to "evergreen" their patents using this unstoppable tactic. Not surprisingly, leading Wall Street analysts predict that use code manipulation will now flourish—that brands "will extract significant [earnings per share] and [net present value] upside from utilization of PUC (Patent Use Code) narrative strategies."[2] Similarly, the FDA's counsel has stated that a "solution" to the problems created by the ruling below "has eluded the agency," as alternative approaches are "a recipe for marketplace confusion" and "complications in terms of intellectual property rights." Pet. 26-27. At a minimum, these statements warrant seeking the Solicitor General's views.

Unable to discount the importance of the question presented, respondents resort to unconvincing arguments that this case is a poor vehicle for resolving it. For example, they now say petitioners' Section viii request eliminated jurisdiction over *their own law-*

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[2] Morgan Stanley Research Europe, *Pharmaceuticals: Potential Selective Upside for Industry Post Prandin Ruling* 2 (Sept. 1, 2010), *available at* http://www.fdalawblog.net/files/morgan-stanley-rpt---puc-decision.pdf.

suit. But petitioners have confirmed with the FDA, in writing, that they are "maintaining [a] [Paragraph IV] certification under protest." Opp. App. 10a. That is sufficient to maintain jurisdiction under 35 U.S.C. § 271(e)(2)(A).

Nor does the interlocutory nature of the decision below warrant denying certiorari. No further factual development is necessary, the legal issue is squarely presented, and this Court often reviews interlocutory rulings involving critical federal issues. Indeed, in *Eli Lilly* this Court granted interlocutory review to decide whether 35 U.S.C. § 271(e)(1) provided a defense to infringement, even though (unlike here) the Federal Circuit had "remanded for the District Court to determine whether in fact [the] condition[s] [for applying the defense] had been met." 496 U.S. at 664. Given the importance of the issues, the Court should do likewise here.

I. Respondents' jurisdictional and vehicular arguments do not withstand scrutiny.

A. Respondents' belated challenge to jurisdiction over their *own* suit lacks merit.

1. After years of litigation over the counterclaim, respondents now say the courts lack jurisdiction over their own lawsuit. But this argument is foreclosed by the governing statute, as construed by this Court. Respondents' lawsuit is authorized by 35 U.S.C. § 271(e)(2)(A), which makes it "an act of infringement to submit * * * [an ANDA] * * * for a drug claimed in a patent or the use of which is claimed in a patent." This provision "creat[es] * * * a highly artificial act of infringement that consists of submitting an ANDA * * * containing a [Paragraph IV] certification." *Eli Lilly*, 496 U.S. at 678. Here, there is no dispute that

Caraco filed an ANDA with a Paragraph IV certification as to every claim of Novo's patent. That created federal jurisdiction. 28 U.S.C. § 1338.

That Caraco later invoked Section viii is irrelevant. Respondents say their patent claim is "subject only to a section viii statement." Opp. 16. Not so. Thanks to their overbroad use code, "FDA declined to allow [petitioners'] section viii carve-out." Opp. 9. But petitioners thereafter confirmed with the FDA, in writing, that they are "maintaining [a] [Paragraph IV] certification under protest." Opp. App. 10a. This is undisputed. And it explains why respondents delayed before raising the jurisdictional theory they now say precludes review.

Respondents' delay speaks volumes about their newfound argument's merit. As the district court admonished their counsel: "[D]on't play games with me." Addendum, *infra*. The games continue.

2. Indeed, respondents have played this game before—on the other side, no less—in the very case they say "conflicts" with the ruling below, but which does no such thing. Opp. 16. As the court there explained: "Novo Nordisk asserts that * * * the filing of an ANDA that *should* include a Paragraph IV Certification constitutes a jurisdictional 'act of infringement' under Section 271(e)(2)(A)." *Novo Nordisk Inc.* v. *Mylan Pharm. Inc.*, 2010 WL 1372437, *8 (D.N.J. Mar. 31, 2010). The court agreed, finding no jurisdiction only because the complaint was "missing * * * an allegation that [the] proposed [carve-out] *has been rejected* by the FDA." *Id.* at *12. Had that occurred, the court "would indeed [have] f[ou]nd that it had jurisdiction to entertain [the] patent infringement action," because "the filing of an ANDA that *should* in-

clude, but does not include, a Paragraph IV certification nevertheless constitutes an act of infringement." *Ibid.* *A fortiori*, jurisdiction exists here, where petitioners *did* invoke Paragraph IV. Opp. App. 10a.

Like their use codes and statements on this case's importance, respondents' jurisdictional positions depend on their convenience. Their newfound view is an "attempt[] to manipulate the Court's jurisdiction to insulate a favorable decision from review." *City of Erie* v. *Pap's A.M.*, 529 U.S. 277, 288 (2000).

B. Respondents' other vehicle arguments are a diversionary tactic.

1. Respondents also say review is unwarranted because the ruling below was "interlocutory." Opp. 18. But no further factual development is necessary, and this Court frequently grants interlocutory review of "important and clear-cut issue[s]" in circumstances such as these. E. Gressman, *et al.*, *Supreme Court Practice* § 4.18, at 281 (9th ed. 2007)(collecting cases).

Indeed, this Court has granted interlocutory review under Hatch-Waxman even when factual development *was* needed. In *Eli Lilly*, the Court reviewed an interlocutory decision that 35 U.S.C. § 271(e)(1) provided a defense to patent infringement in medical device cases, even though the Federal Circuit had "remanded for the District Court to determine whether in fact [the] condition[s] [for applying § 271(e)(1)] had been met." 496 U.S. at 664. The need for further fact-finding—absent here—did not deter review, presumably because the issue was important to the industry and the Federal Circuit's ruling was otherwise the final word. Similar considerations warrant review here.

2. *Eli Lilly* likewise disposes of the notion that review is premature because the ruling below marks "the first appellate decision construing the Hatch-Waxman counterclaim." Opp. 3. That case "raise[d] a question of first impression, namely, whether the noninfringement defense of 35 U.S.C. § 271(e)(1) * * * applies to medical devices." 872 F.2d 402, 404 (Fed. Cir. 1989). Yet this Court granted certiorari—again, presumably because a definitive ruling was needed and percolation was unlikely to generate a split. Cf. *Am. Fed'n of Musicians* v. *Wittstein*, 379 U.S. 171, 175 (1964) (reviewing "an important [question] of first impression"). So too here.

3. Respondents warn against "piecemeal" review (Opp. 18), but the validity issues below are separate and distinct from the counterclaim's meaning. Respondents do not suggest that the case has become moot. Nor could they, given their recent notice of appeal (Opp. 18) and the district court's decision to stay various issues pending appeal. If the invalidity ruling were reversed, moreover, it would likely generate further proceedings involving claims for damages.

4. Respondents' suggestion (at 17-18) that deferring resolution of the question presented would entail "no attendant prejudice to any party" rings especially hollow. But for respondents' new use code, Caraco would have received Section viii approval to market its drug for concededly non-infringing uses years ago —*without further litigation*. Delay will only reward gamesmanship, amplify brands' "incentive to follow Novo's lead," and "subvert[] Section viii" (Pet. 62a, 60a)—which Congress designed to *eliminate* litigation over non-infringing uses. It is therefore perverse for Novo to suggest waiting until distinct issues play out

below. As the *amicus* briefs confirm, review is needed now, to prevent this cycle from repeating itself.

II. Respondents' merits arguments fail to rehabilitate the decision below.

Lacking a persuasive vehicle argument, respondents retreat to the merits. Opp. 19-32. They ignore many of our statutory points, however, and mischaracterize others as "policy-based." Opp. 21. Further, the arguments they do make run headlong into the text and "structure of the * * * Act taken as a whole." *Eli Lilly*, 496 U.S. at 669.

A. Respondents ignore critical textual and structural signals that preclude reading "*an* approved method of use" to mean "*any* approved method of use."

The court below overlooked five textual and structural problems with reading the phrase "*an* approved method of use" to mean "*any* approved method of use." Pet. 29-34. Respondents seize on our acknowledgment that the word "'an,' when qualified by a negative, *can* mean 'any'" (Pet. 30), calling this a "fatal" "concession" (Opp. 22). But they ignore multiple reasons why that meaning is foreclosed *here*.

1. *First*, respondents ignore our showing that the very provision at issue elsewhere uses the term "any" —thus confirming that, *in Hatch-Waxman's counterclaim*, "an" cannot mean "any." Pet. 32.

Second, respondents ignore that using "any" in "negative assertions * * * creates an *emphatic* negative," and thus changes the counterclaim's meaning. Pet. 30-31.

Third, respondents ignore that it takes "strong evidence" to conclude that Congress "enact[ed] provi-

sions" that "create an effective extension of the patent term." *Eli Lilly*, 496 U.S. at 670, 672. That is the effect of the decision below. Pet. 33.[3] But such evidence is lacking here.

Fourth, respondents ignore that the counterclaim places the burden of proof, not on the *brand*, to show that its patent "does claim" an approved use, but on the *generic*, to show what the patent "does not claim." Pet. 31-32. When there is but one FDA-approved use, that is one and the same inquiry. But when there are additional FDA-approved uses, whether the patent claims an approved use is not necessarily an either/or proposition.

2. Nor are the arguments that respondents *do* advance convincing. For example, their reading renders superfluous the counterclaim's language authorizing courts to "*correct or* delete" patent information. Pet. 32-33. Respondents answer that the term "correct" would serve a purpose "[i]f an error were made"—*e.g.*, by listing "the wrong patent number." Opp. 23. But even then the remedy would be "deleting" the patent. Further, inasmuch as generic manufacturers' Paragraph I-IV obligations extend only to listed patents, 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV), brands already have ample incentive to fix incorrect patent numbers. Respondents cannot explain why Congress would authorize a counterclaim so generics could force brands to correct typos.

It is far less strained to read "correct" as authorizing courts to order brands to fix use codes that overstate their patents' scope. "Congress used two terms"

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[3] Respondents' compound patent expired in 2009; their method patent expires in 2018.

—correct *and* delete—"because it intended each term to have a particular, nonsuperfluous meaning." *Bailey* v. *United States*, 516 U.S. 137, 146 (1995). And the fact that respondents' reading renders "correct" superfluous forecloses their suggestion (Opp. 23-24) that the counterclaim addresses only the fact pattern of *Mylan*—where the patent claimed *neither* the listed drug *nor* any method of using it, and the proper remedy was thus to "delete" it. Pet. 32a (Dyk, J.).

Respondents support reading laws "*in pari materia*" (Opp. 22), but reject reading the counterclaim in light of Section viii, which uses similar language. 21 U.S.C. § 355(j)(2)(A)(viii). Finally, they deride as "policy-based" our position that the counterclaim extends beyond *Mylan* (Opp. 21); but as the foregoing makes clear, our arguments are textual and structural.[4]

B. Congress ratified the FDA's definition of "patent information."

The petition presented three independent reasons why the Federal Circuit's reading of "patent information" cannot stand: (1) the FDA read "patent information" to include use codes before 2003, and Congress adopted that reading (Pet. 34); (2) the counterclaim refers to patent information "*submitted* * * * *under* subsection (b) or (c)," not to patent information "*referenced in*" those subsections, and thus includes all FDA-required patent information (Pet. 35); (3) "at a minimum, [the FDA's] interpretation is reasonable,

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[4] Respondents cite *Buckman Co.* v. *Plaintiffs' Legal Committee*, but that case held only that federal enforcement of the FDCA preempted "unpredictable civil liability" under *state* law. 531 U.S. 341, 348, 350 (2001). The counterclaim provides *federal* authority for ordering brands to correct misleading patent information.

warranting *Chevron* deference" (*ibid.*). Respondents blur our first and third points, and ignore the second.

1. As to ratification and *Chevron*, respondents say deference is not warranted because the FDA "did not justify th[e] requirement [to submit use codes] as an interpretation of 'patent information' in subsection (b) or (c) [of Section 505]." Opp. 27. But as Judge Dyk explained, the 2003 final rule "makes clear that the FDA is defining what constitutes 'patent information' for purposes of subsections (b) and (c)." Pet. 34a. Indeed, the FDA fully "explain[ed] why we (FDA) issued the proposal," and "the statutory provisions" supporting it—citing §§ 505(b)(2), 505(b)(1), and 505(c)(2) of the Act. 68 Fed. Reg. at 36676. Similarly, since 2003 FDA Form 3542 has stated that "patent information submitted" with an NDA is "provided in accordance with Section 505(b) and (c)." Pet. 211a. Thus, when Congress referenced "patent information * * * submitted under subsection (b) or (c) of this section," it was adopting the FDA's definition.

Respondents nonetheless focus on events *after* the counterclaim's adoption. Citing FDA comments from *2007*, they say the *2003* rule was based on the FDA's "general rulemaking authority and subsection (j)." Opp. 27. The very pages they cite, however, reiterate that "the basis for requiring a description of each individual method of use for which a patent is submitted for listing" was "discussed in the June 2003 final rule" (72 Fed. Reg. at 21268)—which, as noted, invoked § 505(b) and (c). Moreover, even in 2007 the agency continued to invoke § 505(b). 72 Fed. Reg. at 21268-21689.

In any case, events in 2007 are irrelevant to what Congress ratified in 2003. For that, one must look to

the 2003 final rule and Form 3542. The FDA may be "the sorcerer's apprentice," but "the sorcerer himself" has now spoken (Opp. 28), adopting the agency's prior interpretation.

2. Because Congress ratified the FDA's interpretation, the decision below is wrong even apart from *Chevron*. But since the meaning of "patent information" under the counterclaim is tied to § 505(b) and (c) —which the FDA has undisputed authority to interpret and implement—reading that term to include use code narratives is valid under *Chevron* if reasonable. And it is plainly reasonable for the FDA to require "detailed information related to the approved methods of use," which is "essential" to "review of ANDA * * * applications that do not seek approval for all the approved uses." 68 Fed. Reg. at 36682, 36685.

Respondents dismiss our showing that the decision below threatens the FDA's ability to administer Section viii. But as the FDA's counsel has explained, that decision has caused the agency to "assess[] ways to alter how it handles patent use codes," and "a straightforward solution so far has eluded [FDA]." Pet. 26-27. Thus, the urgency of review is confirmed by the fact that "the majority opinion effectively invalidates the FDA's effort to define 'patent information,'" "[w]ithout even requesting the [FDA's] views." Pet. 63a (Gajarsa, J.).[5]

3. Finally, respondents insist that their revised use code is technically "correct." Opp. 30. But they do not dispute that their use code is *materially misleading*, and in that sense it is incorrect under any

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[5] Caraco cannot effectively sue FDA, which lacks authority to police use codes. Pet. 51a-52a (Dyk, J.); Pet. 24.

definition. http://www.merriam-webster.com/dictionary/correct (defining "correct" as "to make or set right: amend <correct an error>"; "counteract, neutralize"; and "to alter or adjust so as to bring to some standard or required condition"). As the governing regulations explain, to serve its statutory purpose, "the description of the patented method of use" must be both "accurate and detailed." 68 Fed. Reg. at 36682. Yet respondents' new use code "is so broad as to incorrectly suggest that [their] patent generically covers three (3) different FDA-approved methods of use," when "[they] admit[] that the first two (2) uses are not covered." Pet. 68a. Thus, Novo's submission "seriously misrepresents the approved method of use," requiring correction. Pet. 70a.

CONCLUSION

In sum, respondents' arguments do not diminish the importance of the question presented or the need for immediate review. Lest Section viii and the counterclaim be "render[ed] * * * a dead letter" (Pet. 62a), this Court should grant certiorari. Alternatively, the Court should call for the Solicitor General's views.

Respectfully submitted.

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AMICUS CURIAE BRIEF

No. 10-844

In the Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD., ET AL., PETITIONERS

v.

NOVO NORDISK A/S, ET AL.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

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QUESTION PRESENTED

By filing an abbreviated new drug application (ANDA), a manufacturer may seek approval from the Food and Drug Administration (FDA) to market a generic version of a previously approved brand-name drug. The ANDA must address, *inter alia*, each patent that claims a method of using the drug. If the ANDA seeks approval for a use claimed by a patent, it must include a certification that the patent has expired, will expire, is invalid, or would not be infringed by the sale or use of the generic drug. Alternatively, the ANDA applicant may inform FDA that it seeks approval for a method of use that the patent does not claim. To determine whether an ANDA seeks approval for a patented use—and hence whether it includes the required certifications—FDA relies on information describing the relevant patent's scope submitted by the brand-name manufacturer under FDA regulations.

The brand-name manufacturer may sue the ANDA applicant for patent infringement if, *inter alia*, the ANDA seeks approval for a patented use before the relevant patent has expired. The ANDA applicant may respond with "a counterclaim seeking an order requiring the [brand-name manufacturer] to correct or delete the patent information [it previously] submitted * * * on the ground that the patent does not claim either—(aa) the drug for which the application was approved; or (bb) an approved method of using the drug." 21 U.S.C. 355(j)(5)(C)(ii)(I). The question presented is as follows:

Whether an ANDA applicant may assert a counterclaim under Section 355(j)(5)(C)(ii)(I) by alleging that the brand-name manufacturer's patent information does not accurately and precisely describe the method of use claimed by its patent.

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BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

This brief is filed in response to the Court's order inviting the Acting Solicitor General to express the views of the United States. In the view of the United States, the petition for a writ of certiorari should be granted.

STATEMENT

1. a. Under the Federal Food, Drug, and Cosmetic Act, as amended, 21 U.S.C. 301 *et seq.*, the Food and Drug Administration (FDA) regulates the manufacture, sale, and labeling of prescription drugs. To obtain FDA's approval to market a new drug, a manufacturer must submit a new drug application (NDA). 21 U.S.C. 355(b). The NDA must contain, *inter alia*, proposed labeling that describes the uses for which the new drug may be marketed. See 21 U.S.C. 355(b)(1)(F). A drug

approved under the NDA process is often referred to as a "brand-name" drug.

After a brand-name drug's NDA has been approved, and subject to certain periods of NDA exclusivity (see 21 U.S.C. 355(j)(5)(F)), any manufacturer may seek approval to market a generic version. The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, known as the Hatch-Waxman Amendments, establishes a process for submitting an abbreviated new drug application (ANDA) for a generic drug. 21 U.S.C. 355(j). The ANDA approval process does not require the manufacturer to provide independent clinical evidence of safety or efficacy. Instead, the ANDA must generally show, *inter alia*, that the generic drug has the same active ingredient(s) as, and is bioequivalent to, a reference listed drug (RLD), *i.e.*, the brand-name drug to which the proposed generic will be equivalent. 21 U.S.C. 355(j)(2)(A)(ii) and (iv).

b. An ANDA must also explain how the generic drug can be marketed without infringing the NDA holder's patent rights. See 21 U.S.C. 355(j)(2)(vii)-(viii). To facilitate that process, NDA holders submit patent information to FDA, and FDA reprints certain information in *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the "Orange Book." See 21 U.S.C. 355(b)(1), (c)(2) and (j)(7). The patent information published in the Orange Book then serves as a frame of reference for the ANDA.

i. The Hatch-Waxman Amendments require an NDA applicant to submit "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably

be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. 355(b)(1). FDA regulations require the applicant to submit additional information during the NDA approval process. See 21 C.F.R. 314.53. Of particular relevance here, once a new drug is approved, the manufacturer must submit "a description of each approved method of use or indication and related patent claim of the patent being submitted"; identify "the specific section of the approved labeling for the drug product that corresponds to the method of use claimed by the patent submitted"; and provide a "description of the patented method of use as required for publication." 21 C.F.R. 314.53(c)(2)(ii)(P). If a new patent issues after the application is submitted, the NDA applicant must update the patent information it previously submitted to FDA. 21 U.S.C. 355(b)(1) and (c)(2).

FDA "publish[es] in the [Orange Book] the patent number and expiration date of each patent that is required to be, and is, submitted to FDA by an applicant." 21 C.F.R. 314.53(e). "[F]or each use patent," FDA also publishes "the approved indications or other conditions of use covered by a patent" (commonly called a "use code"). *Ibid.* The Hatch-Waxman Amendments do not direct FDA to verify the patent information, and FDA lacks the resources and the patent expertise to do so. See 68 Fed. Reg. 36,683 (2003). Accordingly, FDA does not compare the NDA holder's use codes to the claims of the underlying patent; rather, it plays the "ministerial" role of publishing the patent information as submitted by the NDA holder. *Ibid.*

ii. An ANDA must account for each patent listed in the Orange Book as associated with the RLD. That requirement is easily satisfied when the listed patent has

expired or the ANDA applicant is willing to await approval until the patent expires. See 21 U.S.C. 355(j)(2)(A)(vii)(II)-(III). Otherwise, the ANDA applicant has two choices with respect to a patent claiming a method of using the drug:

In appropriate circumstances, the ANDA applicant may assert that, although the listed patent claims a method of using the RLD, the ANDA applicant does not seek approval of its drug for that use. 21 U.S.C. 355(j)(2)(A)(viii). This assertion is known as a "section viii statement." If an ANDA applicant makes a section viii statement, and the ANDA is otherwise approvable, FDA may approve the ANDA without requiring any further steps relating to the patent. And FDA will approve appropriate labeling for the generic drug that "carves out" information related to the patented use (as described in the use code) from the RLD's existing approved labeling, thus approving the generic drug only for unpatented uses. See 21 C.F.R. 314.94(a)(8)(iv), 314.127(a)(7). Approval with carve-out labeling is only permitted, however, if the drug so labeled will remain safe and effective. See *ibid.* FDA will not approve an ANDA with a section viii statement if the ANDA applicant's proposed labeling includes information related to a method of use claimed by an unexpired patent listed in the Orange Book—*i.e.*, if there is any overlap between the methods of using the drug reflected in (1) the carved-out labeling proposed in the ANDA and (2) the use code in the Orange Book. See 68 Fed. Reg. at 36,682-36,683.

Alternatively, if a section viii statement is inappropriate (because the patent's use code effectively precludes carve-out labeling) or undesirable (because the ANDA applicant wishes to market its drug without carv-

ing out the protected use), the ANDA applicant may certify that the patent "is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the [ANDA] is submitted," 21 U.S.C. 355(j)(2)(A)(vii)(IV), and seek approval for an ANDA that does not include a labeling carve-out. This certification is known as a "paragraph IV certification."

Rather than embroiling FDA in controversies over patent validity and infringement, Congress channeled disputes about the correctness of paragraph IV certifications to the courts. Thus, an ANDA applicant that makes a paragraph IV certification must provide notice to the patent owner, 21 U.S.C. 355(j)(2)(B), which may in turn file a patent infringement suit in district court on the basis of the ANDA alone, without waiting for some other potentially infringing act, see 35 U.S.C. 271(e)(2)(A). If the patent owner sues within 45 days after receiving notice from the ANDA applicant, FDA generally may not approve the ANDA until the court finds the patent invalid or not infringed, or 30 months elapse from receipt of notice from the ANDA applicant. See 21 U.S.C. 355(j)(5)(B)(iii). If the patent owner does not sue within 45 days, FDA may approve the application immediately, *ibid.*, though without prejudice to infringement claims the patent owner might assert when the ANDA applicant produces or markets the generic drug.

c. In 2003, Congress authorized an ANDA applicant defending a patent infringement action to

> assert a counterclaim seeking an order requiring the [RLD NDA holder] to correct or delete the patent information submitted by the holder under

> [21 U.S.C. 355(b) or (c)] on the ground that the patent does not claim either—
>
> (aa) the drug for which the application was approved; or
>
> (bb) an approved method of using the drug.

21 U.S.C. 355(j)(5)(C)(ii) (added by Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, § 1101(a)(2)(C), 117 Stat. 2452). Like the original Hatch-Waxman scheme for paragraph IV litigation, the counterclaim provision assigns FDA no role in deciding the scope or validity of patents, and instead channels such disputes to courts.

2. a. Petitioner Caraco wishes to market a generic version of Prandin®, respondents' brand-name version of the diabetes drug repaglinide. Respondents' patent on the repaglinide compound expired in 2009. Respondents also own a patent (the '358 patent) that will expire in 2018 and that pertains to the combination of repaglinide with another drug, metformin. Claim 4 of the '358 patent claims "[a] method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin." C.A. App. 79.

Petitioner submitted an ANDA seeking approval of a generic version of repaglinide upon the expiration (in 2009) of respondents' patent on the repaglinide compound. When petitioner initially filed its ANDA, respondents' use code for the '358 patent described Claim 4 as pertaining to the "[u]se of repaglinide in combination with metformin to lower blood glucose." Pet. App. 8a. Petitioner's application initially included a paragraph IV certification to the '358 patent, asserting that the patent was invalid or would not be infringed by petitioner's

marketing of generic repaglinide. Respondents filed a timely infringement action, thus delaying FDA's approval of petitioner's ANDA. Petitioner later amended its ANDA to replace the paragraph IV certification to Claim 4 of the '358 patent with a section viii statement that petitioner did not seek approval for use of the repaglinide-metformin combination therapy. Although other matters prevented FDA from immediately approving petitioner's ANDA, FDA indicated that it would approve carve-out labeling that excluded the combination-therapy use (but included, for example, use of repaglinide on its own, known as "monotherapy"). *Ibid.*

Meanwhile, as part of an effort to improve the labeling of oral anti-diabetic drugs (including Prandin®), FDA asked respondents to revise Prandin®'s labeling to "[r]eplace all the separate indications [for use of the drug] (e.g., monotherapy, combination therapy, and initial or second-line therapy) with the following sentence: 'Prandin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.'" C.A. App. 667-668. Respondents complied. About a year later, respondents submitted an amended use code for the '358 patent that tracked the revised indication for Prandin®: "A method for improving glycemic control in adults with type 2 diabetes mellitus." Pet. App. 9a.

Because petitioner was unable to carve out the single approved indication that corresponded to respondents' new use code yet maintain a safe and effective drug, FDA reversed course and disallowed a labeling carve-out.[1] Petitioner then filed a counterclaim against re

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[1] Petitioner states that although it submitted a section viii statement, it also is "maintaining [a] [Paragraph IV] certification under

spondents in the pending infringement litigation, seeking an order directing respondents to revert to the old use code, which would make clear that the '358 patent does not claim the entirety of the single approved indication.

b. In a series of orders, the district court held that petitioner's counterclaim was proper and that respondents' new use code was overbroad. Pet. App. 65a-96a. The court explained that the counterclaim provision was designed to address the possibility that an ANDA applicant "could be seriously disadvantaged by an incorrect Use Code narrative." *Id.* at 93a. On the merits, the court agreed with petitioner that respondents' new "use code fails to identify with any specificity whatsoever the patented method and, read literally, suggests that [the '358] patent covers any method of improving glycemic control in adults with Type 2 diabetes." *Id.* at 71a. The district court accordingly enjoined respondents to "correct * * * [their] inaccurate description of the '358 patent by submitting to FDA [a use code] that * * * describes claim 4 of the '358 patent * * * as covering the 'use of repaglinide in combination with metformin to lower blood glucose.'" *Id.* at 65a-66a.

3. The court of appeals reversed. Pet. App. 1a-52a.

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protest." Pet. Reply Br. 4 (quoting Br. in Opp. App. 10a) (brackets in original). FDA does not recognize certifications "under protest," nor does it permit a simultaneous paragraph IV certification and section viii statement to the same claim of a particular patent. If an ANDA applicant's latest submission to FDA was a section viii statement—something FDA will not publicly confirm or deny with respect to petitioner's ANDA because pre-approval applications to FDA are confidential, see 21 C.F.R. 314.430(d)(1)—then the applicant's ANDA would currently be considered to contain a section viii statement rather than a paragraph IV certification.

a. The court of appeals first discussed the counterclaim provision's reference to a patent that "does not claim * * * an approved method of using the drug." 21 U.S.C. 355(j)(5)(C)(ii)(I). The court interpreted that language to apply only when the patent does not claim *any* approved method of using the drug. Pet. App. 11a-12a. The court thus held that the counterclaim mechanism is unavailable if (as here) the listed patent claims at least one approved method of using the drug, even if the NDA holder's use code misleadingly suggests that the patent claims other approved methods of use as well.

The court of appeals found that conclusion to be further supported by the counterclaim provision's authorization of "an order compelling 'the holder to correct or delete *the patent information* submitted by the holder under subsection (b) or (c).'" Pet. App. 15a (quoting 21 U.S.C. 355(j)(5)(C)(ii)(I)). The referenced provisions, 21 U.S.C. 355(b) and (c), require NDA applicants to submit only the patent number and expiration date of the relevant patents, not the more detailed information (including the use code) that is mandated by FDA regulations. *Ibid.* The court of appeals inferred from that fact that "the [Hatch-Waxman Amendments] defined the term 'patent information' as the patent number and the expiration date." *Ibid.* (internal quotation marks and citation omitted). The court concluded on that basis that the only relief available under the counterclaim provision is an order directing the NDA holder to delete or correct a patent number or expiration date, and that the provision is not concerned with errors or misrepresentations in a use code. *Id.* at 15a-16a.

b. Judge Clevenger concurred. Pet. App. 19a-21a. He agreed with the court's textual analysis, though he was skeptical that paragraph IV litigation would resolve

the parties' dispute over the accuracy of respondents' use code. *Id.* at 19a. He also expressed the view that FDA's request for changes to Prandin®'s approved labeling had precipitated the problem here, and that respondents had done "nothing that was illegal or forbidden" when they "changed [the] use code to match the new PRANDIN® indication." *Id.* at 19a-20a.

c. Judge Dyk dissented. Pet. App. 22a-52a. He would have read the phrase "the patent does not claim * * * an approved method of using the drug" to encompass the situation in which information in the Orange Book incorrectly asserts that the patent claims a particular approved method of use. *Id.* at 40a. Judge Dyk further explained that when the counterclaim provision was enacted in 2003, FDA had already "adopted detailed requirements for the submission of 'patent information' for both drugs and methods," including use codes, *id.* at 33a, and "Congress was well aware of this regulatory interpretation of 'patent information' when it enacted the counterclaim provision," *id.* at 36a. Judge Dyk therefore would have read the term "patent information" in the counterclaim provision to encompass the "method of use" information that is at issue in this case. *Id.* at 39a. He also observed that "there is absolutely nothing in the statute or regulations that required [respondents] to change the use code to track [the] new indication" for oral anti-diabetic drugs. *Id.* at 47a-48a.

4. The court of appeals denied rehearing en banc. Pet. App. 53a-56a. Judge Gajarsa, joined by Judge Dyk, dissented. *Id.* at 57a-64a. They concluded that the court's construction of the counterclaim provision "seriously undermines Section viii" and "eliminates the careful balance Congress has struck between encouraging pharmaceutical discoveries and ensuring that the Ameri-

can people have access to low cost generic drugs." *Id.* at 59a.

5. Proceedings in the underlying infringement litigation resumed in district court after the court of appeals' ruling. After a bench trial, the district court held the '358 patent invalid for obviousness and unenforceable for inequitable conduct before the Patent and Trademark Office. Br. in Opp. App. 14a. Respondents' appeal from that judgment is pending. *Novo Nordisk A/S* v. *Caraco Pharm. Labs., Ltd.*, No. 2011-1223 (Fed. Cir.) (filed Feb. 23, 2011).

DISCUSSION

Under the Federal Circuit's decision, a brand-name manufacturer can effectively preclude generic competition by submitting an overbroad description of its method-of-use patent to FDA. Congress enacted the counterclaim provision at issue here to combat precisely that sort of manipulation. The court's ruling significantly impairs ANDA applicants' ability to secure FDA approval for their products, and hence deprives consumers of the full benefit of generic competition. There will be no opportunity for a circuit split to develop because the counterclaim is available only in patent infringement actions, see 21 U.S.C. 355(j)(5)(C)(ii)(I), as to which the Federal Circuit has exclusive appellate jurisdiction, see 28 U.S.C. 1292(c)(1), 1295(a)(1). The petition for a writ of certiorari should be granted.

A. The Federal Circuit's Decision Is Incorrect

The court of appeals' decision is incorrect for three related reasons. First, the court held that the counterclaim mechanism is available only when a patent listed in the Orange Book does not claim *any* "approved method of using" an approved drug. In fact, the text

and purposes of the provision indicate that a counterclaim may be asserted if the NDA holder's use code misleadingly suggests that the patent covers the *particular* method of use for which the ANDA applicant seeks approval, even if the patent does cover a different method of use. Second, the court gave an unduly restrictive reading to the phrase "patent information submitted by the [NDA] holder under [21 U.S.C. 355(b) or (c)]." Use codes are literally "patent information," and by regulation they are "submitted * * * under" the specified subsections. Third, the court's interpretation of the counterclaim provision subverts Congress's effort to create a meaningful judicial check on NDA holders' exaggerated claims of patent protection.

1. The statute authorizes counterclaims "on the ground that the patent does not claim either (aa) the drug for which the application was approved; or (bb) an approved method of using the drug." 21 U.S.C. 355(j)(5)(C)(ii)(I). It is undisputed in this case that requirement (aa) is satisfied because Claim 4 of the '358 patent does not claim a compound (*i.e.*, "the drug for which the application was approved"). To satisfy requirement (bb), an ANDA applicant must identify an approved method of using the drug—presumably the method of use for which the ANDA applicant seeks approval—that the relevant patent does not claim. To be sure, even if those requirements are satisfied, a court cannot order the NDA holder to "correct or delete" its use code if that use code accurately reflects the limited scope of the patent's coverage. An order to "correct or delete" the patent information is appropriate, however, if the use code misleadingly suggests that the patent claims approved methods of use that it does not actually cover. Petitioners therefore properly invoked the coun-

terclaim provision by alleging that, contrary to the apparent implication of the amended use code that respondents submitted to FDA, the '358 patent does not claim the use of repaglinide as monotherapy, which is "an approved method of using the drug."

The court of appeals, by contrast, held that the counterclaim provision is available only when the relevant patent does not claim *any* approved method of using the drug. Pet. App. 11a-12a. On that view of the statute, petitioners' counterclaim failed because the '358 patent claims the use of repaglinide in combination with metformin. See *ibid.* But as Judge Dyk explained in dissent below, the phrase "*an* approved method" is naturally used to refer to a *particular* approved method. *Id.* at 41a-42a (citing *Webster's Third New International Dictionary* 1 (2002)). And as between the two textually plausible interpretations of the disputed statutory language, the more flexible reading is superior because (as discussed below) the type of misrepresentation alleged in this case directly impedes the effective implementation of the Hatch-Waxman scheme.

2. The court of appeals also erred in holding (Pet. App. 15a-17a) that the "patent information" that may be corrected or deleted through the counterclaim provision is limited to the patent number and expiration date. A use code is "patent information" within any usual understanding of that term because it is "information"—a "description of the patented method of use," 21 C.F.R. 314.53(c)(2)(ii)(P)(3)—about a "patent."

The regulatory backdrop against which Congress acted reinforces the natural reading of the statutory text. Shortly before the counterclaim provision was enacted, FDA promulgated regulations specifying what "patent information" an NDA applicant must submit.

Pet. App. 16a (citing 21 C.F.R. 314.53). Those regulations, entitled "Submission of Patent Information," require NDA applicants to submit descriptions of the uses claimed by their method-of-use patents. 21 C.F.R. 314.53(c)(2)(i)(O) and (ii)(P); see 68 Fed. Reg. at 36,703. Congress was fully aware of that recent regulatory action when it enacted the counterclaim provision later in the same year. See, *e.g.*, 149 Cong. Rec. 15,516 (2003) (statement of Sen. Schumer) ("In fact, when the FDA actually talked about closing these loopholes, it was made clear that legislation would be needed to finish the job.").

Use codes are also properly characterized as being "submitted * * * under subsection (b) or (c) of this section" (*i.e.*, 21 U.S.C. 355(b) or (c)). To be sure, the only patent information that Sections 355(b) and (c) *require* to be submitted is the patent number and expiration date. But the counterclaim provision does not refer to patent information "required by" or "specified in" Sections 355(b) or (c), and the actual statutory language encompasses a broader range of information. Sections 355(b) and (c) lay out the entire process for seeking and obtaining approval for an NDA, and for providing updates to FDA after the drug is approved. In that context, "under" is best read to mean "in a proceeding subject to or governed by" Sections 355(b) and (c). Cf. *Ardestani* v. *INS*, 502 U.S. 129, 135 (1991) (reaching similar conclusion). The patent information encompassed by the counterclaim provision (*i.e.*, the information "submitted * * * under" Sections 355(b) and (c)) thus includes everything FDA requires NDA holders to

submit in the course of seeking and maintaining approval of an NDA—including the use code at issue here.[2]

3. The court of appeals' decision also hinders the effectuation of Congress's purposes in enacting the counterclaim provision. Shortly before the counterclaim provision was enacted, FDA had issued a final rule specifying the patent information an NDA applicant must submit. FDA explained that, because it lacks the expertise and resources to resolve questions of patent law, it would "rely on the description of the approved use provided by the NDA holder or patent owner in the patent declaration and listed in the Orange Book" when evaluating a generic manufacturer's request for carve-out labeling. 68 Fed. Reg. at 36,682. FDA acknowledged that its reliance on NDA holders might tempt them "to submit inappropriate patent information * * * to delay generic competition." *Id.* at 36,683. It explained, however, that "[a] fundamental assumption of the Hatch-Waxman Amendments is that the courts are the appropriate mechanism for the resolution of disputes about the scope and validity of patents." *Ibid.* Accordingly, FDA decided—for the same reasons that prompted it to rely on NDA holders in the first place—not to create an administrative process for challenging NDA holders' patent submissions, but instead to maintain its "ministerial" role in the patent-listing process. *Ibid.*

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[2] We do not understand the Federal Circuit to have held that FDA lacks authority to collect patent information beyond the patent number and expiration date. Regardless of the proper construction of the counterclaim provision, FDA's broad regulatory authority includes the power to require NDA applicants proceeding under 21 U.S.C. 355(b) and (c) to submit information relevant to drug approval. See 21 U.S.C. 371(a).

Later that year, Congress enacted the counterclaim provision. As a leading proponent of the provision explained, the counterclaim provision built on FDA's rulemaking by supplying a mechanism for judicial resolution of disputes about the accuracy of the patent information that FDA had recently required NDA holders to submit. See *Legislative and Regulatory Responses to the FTC Study on Barriers to Entry in the Pharmaceutical Marketplace: Hearing Before the Senate Comm. on the Judiciary*, 108th Cong., 1st Sess. 19 (2003) (statement of Sen. Schumer) ("The bill provides a critical complement to the work the FDA has done in clarifying its regulations on patent listing, but it goes much further."); 149 Cong. Rec. 31,200 (2003) (statement of Sen. Schumer) ("[T]he provisions enforce the patent listing requirements at the FDA by allowing a generic applicant * * * to file a counterclaim to have the brand drug company delist the patent or correct the patent information in FDA's Orange Book.").

The practical effect of the court of appeals' decision, however, is to preclude judicial enforcement of FDA's directive that NDA holders accurately describe their method-of-use patents. Far from "enforc[ing] the patent listing requirements at the FDA," the counterclaim provision as construed by the Federal Circuit applies only when an NDA holder misstates information that is specifically required by the statute. That result is especially unwarranted because submission of an overbroad or otherwise misleading use code can cause the same practical harm (unjustified delay in a generic drug's entry into the market) as does the listing of a patent that claims *no* approved uses of the relevant drug.

B. This Court's Review Is Warranted

1. The Federal Circuit's decision makes it easier for brand-name manufacturers to disrupt and delay the entry of generic competitors

The Federal Circuit's decision prevents the courts from performing their traditional function of resolving disputes about the scope of patent rights, while leaving no alternative decision-maker to fill their shoes. The unavailability of a judicial remedy harms consumers of prescription drugs by making it easier for NDA holders to extend their periods of exclusivity by submitting inaccurate or misleading patent information.

a. Because respondents continue to maintain that their use code appropriately describes Claim 4 of the '358 patent, FDA cannot direct that the use code be changed without making a substantive judgment about the scope of that patent's coverage. But FDA has neither the resources nor the expertise to make such judgments, and to do so would assume precisely the substantive role the agency forswore in its 2003 rulemaking. See 68 Fed. Reg. at 36,683. Congress embraced that sound policy choice in 2003 when it created the counterclaim provision to authorize judicial resolution of disputes over the scope of use patents.

To be sure, even without engaging in substantive patent analysis, FDA might be able to take additional administrative steps to increase the accuracy and precision of patent information submitted by NDA holders. For example, FDA could amend the instructions accompanying the patent information declaration to state explicitly that a drug's approved indication may be recited as a patent use code only if the indication precisely describes the method of use claimed by the patent. FDA

could even abandon the use code approach and instead seek a certification from the NDA holder regarding whether specific carve-out labeling proposed by an ANDA applicant would infringe the NDA holder's patent. Any such measures are likely to be inefficacious, however, if no judicial check is available to determine whether the information an NDA holder submits accurately describes the scope of its use patent's coverage. The court of appeals' decision removes that judicial check.

b. Contrary to the court of appeals' suggestion, (Pet. App. 13a-14a), paragraph IV litigation is not an adequate substitute for the counterclaim provision. The ANDA applicant cannot carve out an infringing use and then make a paragraph IV certification; the two are mutually exclusive. Cf. 59 Fed. Reg. 50,347 (1994). Rather, to submit a paragraph IV certification, the ANDA applicant must propose labeling the same as the RLD's, and must assert that the RLD NDA holder's patent "is invalid or will not be infringed" (21 U.S.C. 355(j)(2)(A)(vii)(IV)) even if the generic manufacturer uses that labeling. So long as the NDA holder's patent covers *some* approved method of using the approved drug, the proposed labeling will be infringing. The court in paragraph IV litigation therefore will have no occasion to determine whether some hypothetical carved-out labeling would infringe the NDA holder's method-of-use patent, or whether the use code submitted by the NDA holder accurately and precisely describes the method of use claimed in the patent.

c. Lower-priced generic drugs save consumers many billions of dollars each year. See, *e.g.*, Fed. Trade Comm'n, *Generic Drug Entry Prior to Patent Expiration: An FTC Study* 9 (July 2002). Carve-out labeling

approved based on a section viii statement is an important path to approval for generic drugs. FDA has informed us that in Fiscal Year 2010 it approved 11 ANDAs with carve-out labeling. Of these, the top three brand-name equivalents alone had nearly $6 billion in annual sales. A number of factors may affect the percentage of those sales that is diverted to generic drugs. But even if that fraction is modest, it is reasonable to estimate that consumers save billions of dollars each year from approval of ANDAs with section viii statements. Although many NDA holders might not submit inappropriate use codes, the trade sources petitioners cite (see Pet. 23) suggest that NDA holders are aware of the tactic. By eliminating the only judicial check on that tactic, the Federal Circuit's decision will likely impair the market entry of generic drugs, with consequent harm to consumers.

2. ***This case is a suitable vehicle for resolving the question presented***

a. For two reasons, this case is a suitable vehicle for addressing the proper scope of the counterclaim provision. First, the Court can be confident of reaching the question presented. Petitioner concedes that the '358 patent was appropriately listed in the Orange Book; its sole contention is that respondents' use code is inappropriate and should be corrected. Second, the history of petitioner's ANDA makes clear that a judicial order directing respondents' to "correct" their use code would have tangible benefits for petitioners. When respondents' prior use code was in effect, FDA stated that it would approve a repaglinide ANDA with a section viii statement; the agency reversed course only after respondents submitted a new use code.

b. Respondents (Br. in Opp. 30-31) and Judge Clevenger below (Pet. App. 19a-20a) suggest that FDA has categorically authorized NDA holders to submit use codes that track the approved indications for their drugs, even when a particular approved indication does not accurately describe the method of use claimed in a listed patent. That is incorrect. FDA regulations require an NDA applicant, upon approval of its new drug, to submit a "description of the patented method of use as required for publication" in the Orange Book. 21 C.F.R. 314.53(c)(2)(ii)(P)(3). FDA's instructions accompanying the declaration form on which the NDA holder supplies patent information permit using the approved indication as a use code *if* the approved indication appropriately describes the scope of the patent. But neither the regulations nor the form indicates that the approved indication will *always* constitute an appropriate "description of the patented method of use."

In any event, the question that warrants this Court's review is whether the counterclaim provision may be used to challenge an allegedly deficient use code. The Court can decide that question without determining whether respondents' own use code was deficient. If the court of appeals had held that petitioner's challenge to respondents' use code was cognizable under the counterclaim provision, but that the challenge failed on the merits because the use code conformed to FDA's instructions, FDA could respond to the decision administratively by revising the instructions. See p. 17, *supra*. Even if FDA makes such revisions, however, the court of appeals' actual holding will deprive generic manufacturers of any opportunity to persuade a court that an NDA holder's use code misdescribes the relevant method-of-use patent. And FDA cannot fill that reme-

dial gap administratively without undertaking the type of substantive patent analysis that it has heretofore viewed as beyond its competence. See pp. 15-16, *supra*.

c. The case is not moot and is not likely to become moot. Petitioner's ANDA cannot be approved absent (1) relief under the counterclaim provision, (2) expiration of the '358 patent many years from now, or (3) a paragraph IV certification to Claim 4 of the '358 patent. Approval subject to a paragraph IV certification cannot presently afford petitioner the relief it seeks here. Although the district court held the '358 patent invalid and unenforceable, respondents have appealed that ruling. If petitioner marketed repaglinide under an ANDA approved subject to a paragraph IV certification, a reversal by the Federal Circuit would likely expose petitioner to significant infringement liability. By contrast, if petitioner's ANDA is approved subject to a section viii statement and carve-out labeling, then the product would be less likely to infringe the '358 patent.

Of course, if the Federal Circuit ultimately affirms either the district court's invalidity or unenforceability determination, and that decision becomes final and unreviewable, the '358 patent will be no obstacle to petitioners' marketing of their generic drug. The question whether respondents' current use code accurately describes the patented method of use would then be of no continuing importance. The parties have informed us, however, that, if this Court grants the petition, they will jointly move to stay proceedings in the court of appeals pending the Court's decision on the merits.

3. Respondents' jurisdictional objection lacks merit

Respondents contend that the district court lost subject matter jurisdiction over petitioner's counterclaim

when petitioner amended its ANDA to replace its paragraph IV certification with a section viii statement. See Br. in Opp. 14-17. Whether or not the premise of that argument is accurate, see note 1, *supra*, respondents are incorrect as a legal matter.

The dispute over respondents' use code for the '358 patent is a live controversy under Article III because the resolution of that question will determine whether petitioner may proceed with a section viii statement. See pp. 7-8, *supra*. Because the counterclaim provision creates a federal cause of action, the district court had federal-question jurisdiction under 28 U.S.C. 1331 or patent-law jurisdiction under 28 U.S.C. 1338. And the Federal Circuit had appellate jurisdiction because the district court's jurisdiction over respondents' original infringement suit was based on 28 U.S.C. 1338. See 28 U.S.C. 1292(c)(1), 1295(a)(1).

The counterclaim mechanism is available whenever "an owner of the patent * * * brings a patent infringement action against the applicant." 21 U.S.C. 355(j)(5)(C)(ii)(I). That prerequisite (whether jurisdictional or not) was satisfied here. All agree that the district court had jurisdiction over respondents' infringement action when it was filed, and that the infringement action was pending when petitioner filed the counterclaim.

Whatever effect any amendments to petitioner's ANDA may have had on respondents' infringement action—a question now before the Federal Circuit on which we express no view—nothing in the Hatch-Waxman Amendments states that the counterclaim becomes unavailable simply because post-filing events render the initial infringement suit non-justiciable. Absent any statutory directive to that effect, this case is subject to

the general rule that "[a]s long as a court has jurisdiction, it may hear and render a separate judgment on a counterclaim even if the opposing party's claim has been [or should have been] dismissed." 3 James W. Moore, *Moore's Federal Practice* § 13.95, at 13-91 (3d ed. 2011); cf. 28 U.S.C. 1367(c)(3) (permitting district court to exercise supplemental jurisdiction over remaining claims even after it "has dismissed all claims over which it has original jurisdiction.").

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

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AMICUS CURIAE BRIEF

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IN THE

Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD. AND SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Petitioners,

v.

NOVO NORDISK A/S AND NOVO NORDISK, INC.,
Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF FOR APOTEX, INC. AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

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QUESTION PRESENTED

When the Food & Drug Administration (FDA) approves a drug for multiple uses, the Hatch-Waxman Act allows generic drug makers to avoid contested patent litigation by marketing generic versions of the drug solely for non-patented uses. The FDA lacks the authority and expertise needed to verify the patent information submitted by name-brand drug companies, however, so it defers to their descriptions of the scope of their patents. Such companies can therefore block the approval of generic drugs by submitting overbroad patent descriptions to the FDA, effectively extending their patents to cover non-infringing uses. To combat this problem, the Act allows a "counterclaim seeking an order requiring the [patent] holder to correct or delete the patent information submitted by the holder * * * on the ground that the patent does not claim * * * an approved method of using the drug." 21 U.S.C. § 355(j)(5)(C)(ii)(I). In a 2-1 decision that conflicts with this Court's precedents and recent D.C. Circuit authority, the Federal Circuit held that the counterclaim provision effectively authorizes only "delet[ing]" improperly listed patents, but not "correct[ing]" information that misrepresents the scope of the approved uses claimed by a patent. That ruling expressly invalidates longstanding FDA regulations defining "patent information," which the FDA deems "essential" to administering the Act, without seeking the agency's views. The question presented is: Whether this counterclaim provision applies where (1) there is "an approved method of using the drug" that "the patent does not claim," and (2) the brand submits "patent information" to the FDA that misstates the patent's scope, requiring "correct[ion]."

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INTEREST OF *AMICUS CURIAE*

Amicus curiae Apotex, Inc. is a global generic drug company that frequently files Abbreviated New Drug Applications (ANDAs) seeking U.S. FDA approval to market its drugs and frequently uses "Section viii" statements to carve out information from FDA labels. Annually, in the U.S., Apotex is engaged in dozens of patent lawsuits under the Hatch Waxman Act "HWA", 21 U.S.C. 355(j) et seq. Apotex files this brief because, without correction, the underlying panel decision will gut the Act's "section viii" approval process, which Congress designed as an *alternative* to Hatch-Waxman litigation.[1]

INTRODUCTION

Apotex fully supports the Petitioners. The Federal Circuit panel majority's reading of the Hatch-Waxman Act's counterclaim provision is contrary to the Act's text, structure, legislative history, and purpose. The panel decision is fundamentally flawed and will result in expensive, time-consuming, and complex patent litigation that can all be avoided by reinserting the plain statutory language that the panel judicially redacted. Judge Dyk's dissent in the

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[1] Counsel of Record for all parties have received timely notice of the intent to file this brief, and all parties have consented to the submission of this brief. Thus, no motion for leave to file is required. The parties' letters of consent to the filing of this brief have been filed with the Clerk. Pursuant to this Court's Rule 37.6, *amicus curiae* states that no counsel for a party wrote this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person or entity, other than the *amicus curiae*, its members, or its counsel, has made a monetary contribution to this brief's preparation or submission.

panel decision and Judges Gajarsa's and Dyk's dissent from the denial of the petition for panel rehearing or rehearing en banc both noted that gamesmanship is in play, not actual controversy over the facts. See, 601 F.3d 1359, 1368 (panel decision); 615 F.3d 1374, 1377 (petition for rehearing en banc denied).

As Judge Dyk noted, in "adopting Novo's disingenuous argument blam[ing] the FDA," the majority overlooks "the manipulative nature of Novo's actions." 601 F.3d at 1380. This manipulation—causing the FDA to reject approval of a drug that Novo concedes would have been marketed for only non-infringing uses—is unconscionable. And now that the path for gaming the Act is clear, it will be followed by brand after brand, depriving sick patients of needed cost-effective drugs. The majority's reasoning effectively: wrote out language in the statute; deprives the FDA of authority to require patent descriptions; and renders obsolete a long-established regulatory system that has benefitted generic drug applicants innumerable times.

STATEMENT

The HWA provides the framework for filing generic drug applications ("ANDA's") and for quickly litigating potential patent disputes in expeditious manners. HWA follows a typical pattern: the ANDA is filed, the so-called Paragraph IV Notice Letter detailing the basis of non-infringement or invalidity is sent to the brand, which then has 45-days to sue for patent infringement. A timely filed suit invokes an automatic statutory 30-month stay that bars the FDA from approving the generic company's ANDA. The 30-month stay provides time for the district court

to vet out the patent issues before the generic company launches, but provides for an end-date of that injunction. But-for the 30-month stay (and for another reason not relevant here), the FDA normally approves the ANDA and permits a launch.

To avoid patent infringement and to avoid unnecessary delays to generic drug approval via the automatic 30-month stay, Congress enacted the so-called "Section viii" provision to allow generic companies to "carve out" parts of a label; the carve-out provision allows a generic company to seek FDA approval for something less than what the brand company has FDA approval to do. The panel decision effectively gutted it because it places the onus on the FDA to take action that the FDA has repeatedly said it will not take because it lacks the necessary expertise and resources (and courts have consistently upheld that determination). Furthermore it now requires generic companies to litigate expensive and all-consuming cases for which a previous statutory right existed to avoid having to do.

SUMMARY OF ARGUMENT

The panel decision mistakenly allocated the blame for gamesmanship on the FDA. When the brand company plays the game, it's apparently the FDA's fault. The FDA and Courts below admit that FDA cannot referee in the first place.

The panel decision also gutted statutory language by judicially redacting language out of the statute. By doing so, the panel wrongly reviewed full-bore patent litigation as an allowable, efficient, and effective tool to vet out patent issues. Left uncorrected, the court has created even further gamesmanship tools.

ARGUMENT

When a branded drug company has a patent on one of several FDA approved uses of a drug, this does not prevent generic competition on the other unpatented, approved uses. In those circumstances, the Act permits generics to file a "Section viii" statement indicating that it is not seeking approval to market the drug for any of the approved uses covered by the branded company's method-of-use patents. *See* 21 U.S.C. 355(j)(2)(A)(viii).[2] The Section viii process is important because it speeds the approval and marketing of a lower cost generic drug if there is no enforceable patent in issue.

For example, assume a brand company has an FDA approved psychiatric drug X to treat: (i) depression; (ii) social agoraphobia; (iii) fear of heights; and (iv) controlling anger. The original drug approval and patent covered the depression indication. Later patents and approvals were for the other indications. Now, assume the original patent on drug X and its depression indication are about to expire. It is perfectly permissible and the plain statutory language authorizes the generic company to file its ANDA seeking only approval for the depression indication, which will be unpatented soon. The

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[2] See, Shashank Upadhye, Generic Pharmaceutical Patent and FDA Law, Section 10:6, 10:7 (Thomson West, 2010 Ed.) (Westlaw database: GENPHARMA) ("Generic Pharmaceutical") for a detailed example of how Section viii statements are used. The author of this Brief is a recognized expert in the generic – brand patent field. *FTC v. Bisaro*, 2010 WL 4910266, at *2 (D.D.C., 2010)("From February 2 through March 3, 2009, FTC staff had approximately four conversations with Apotex's Vice President, who is a published expert in the field of generic drug patent and FDA law.").

generic company files Section viii statements to "carve out" (redact) indications (ii) through (iv) and to explicitly not seek approval for those other still-patented indications. Congress intended this via Section viii.[3] Indeed, because the generic drug applicant carves out still-patented indications, it specifically avers that it does not want FDA approval for those omitted indications.

Because FDA rules require brand companies to create and file the so-called Use Code descriptions, a proper Use Code would state that, "Drug X for the use and treatment of depression, social agoraphobia, fear of heights, and controlling anger/rage." But if the brand company creates a Use Code description that states, "Drug X for the treatment of mental

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[3] *Purepac Pharmaceutical Co. v. Thompson*, 354 F.3d 877, 880 (D.C. Cir. 2004) ("A section viii statement indicates that a patent poses no bar to approval of an ANDA because the applicant seeks to market the drug for a use other than the one encompassed by the patent."); see also, *Apotex, Inc. v. Food & Drug Admin.*, 393 F.3d 210, 213-214 (C.A.D.C.,2004)("Before turning to the factual background of the present dispute, we note that the four types of certifications enumerated in 21 U.S.C. § 355(j)(2)(A)(vii) are not the only mechanisms by which an ANDA applicant can address a potentially relevant patent. A generic company can instead submit a statement pursuant to 21 U.S.C. § 355(j)(2)(A)(viii) ("section viii statement"). A section viii statement asserts that a patent does not prevent FDA from approving the company's ANDA because the ANDA applicant seeks to market the drug for a use other than that covered by the patent. See 21 U.S.C. § 355(j)(2)(A)(viii). As we have previously explained, applicants use paragraph IV certifications to challenge the validity of applicable patents, whereas they submit section viii statements to assert that patents do not apply. ANDA applicants who submit section viii statements are not eligible for generic marketing exclusivity pursuant to 21 U.S.C. § 355(j)(5)(B)(iv)."(internal citations omitted).

health", then under the panel's decision, the generic company has no recourse except to file the so-called Paragraph IV certification and engage in costly litigation and use up scarce judicial resources to prove that the patent is not infringed because the generic company now proves what its label reflects: it does not want approval for patented indications and does not infringe. Here, the brand uses code prohibits the generic drug company from carving out the other indication because they are not present. In later Para IV litigation the generic drug company would need to disprove that is not marketing the drug for the still patented indications.

Recourse to FDA is not available because the FDA and the Courts stated *ad nauseum* that FDA's role in Orange Book maintenance is simply ministerial. It does not and will not police Orange Book listings. It lacks the requisite expertise, resources, and statutory authority. The brand company could further game the system to include a Use Code for Drug X stating, "the use of Drug X for the treatment of any ailment or health issue," which would encompass every malady heretofore known. FDA subjectively knows that the Use Code is ridiculous but is objectively powerless to do anything. Now, according to the panel majority below, the affected generic company is powerless to do anything to force the brand company to change the code back to something more appropriate.

I. The Panel Erred By Concluding That "Regular" Paragraph IV Litigation Is An Effective Tool to Vet Out the Patent Issues

The panel majority below correctly recognized that the result of its decision is that patent litigation that

ought not to be brought in the first place will now be housed within the so-called Paragraph IV litigation scheme. 601 F.3d at 1365. That litigation allows the generic company to prove that its generic drug use "will not cause infringement of the patented use." 601 F.3d at 1365. The panel then wrongfully allocated the burden of non-infringement to the generic company whereas this Court has squarely placed the burden of infringement proof on the patentee. *Price v. Kelley*, 154 U.S. 669 (1881).

The Caraco case is not even one where the patentee presented a *prima facie* case of infringement and shifted the burden to Caraco to rebut the infringement.[4] Here, Caraco specifically excluded the patented indications from its label. The panel, however, without one iota of infringement proof, shifted the burden to Caraco (as with any future generic manufacturer) to disprove infringement:

> This court recognizes that a broad use code covering all uses of a pharmaceutical could require generic manufacturers to prove specifically that their use will not overlap with and infringe the patented use. This proof, under Hatch-Waxman procedures, will take the form of a Paragraph IV lawsuit. In that context, the generic may provide proof that their use will not cause infringement of the patented use. This

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[4] Method-of-use patents are usually enforced through 35 U.S.C. §271(b) – Indirect Infringement, especially for inducement to infringe. This Court is currently reviewing the Federal Circuit's standard of inducement to infringe (the requisite state of mind of the inducer) in *Global Tech Appliances v. SEB*, SA, Supreme Court Docket No. 10-006 (set for argument 23 Feb. 2011). See also, Generic Pharmaceutical Sections for a discussion on indirect infringement.

> court perceives that the Hatch-Waxman Act will thus ensure that a generic drug for non-patented purposes will not be used for patented purposes via a simple section viii certification. Instead, the generic manufacturer will need to alleviate the risk of infringement or induced infringement in a proceeding that fully tests for infringement and its implications, including potential health and safety risks.

601 F.3d at 1365.

Accordingly, the generic company is left to prove that it will *not* infringe. This is contrary to law.

More generally, patent litigation under the so-called Paragraph IV scheme is not an effective tool to vet out this omitted indication patent issues. First, as with any patent litigation, the litigation is expensive, time consuming, and taxes scarce judicial resources. See, *Blonder-Tongue Labs v. Univ. of Illinois Found.*, 402 U.S. 313, 334 (1971)("the expense of defending a patent suit is often staggering to the small businessman."); *Schering-Plough Corp. v. F.T.C.*, 402 F.3d 1056, 1075 (C.A.11, 2005)("Patent litigation breeds a litany of direct and indirect costs, ranging from attorney and expert fees to the expenses associated with discovery compliance. Other costs accrue for a variety of reasons, be it the result of uncompromising legal positions, differing strategic objectives, heightened emotions, lawyer incompetence, or sheer moxie."); *Marctec, LLC v. Johnson & Johnson*, 2010 WL 680490, at *6 (S.D.Ill., 2010)("According to a 2007 American Intellectual Property Law Association ("AIPLA") survey, the average total cost of patent infringement litigation where more than $25 million is at risk (considering 419 respondents throughout the United States) was $5.5 million.").

Generic companies have vastly different marketing programs than brand companies. Brand companies have no effect on the generic company's putative infringement. Brand companies "detail" the brand drug to doctors, traditionally by visiting doctor offices, offering tchotchkes like pens, mugs, toys, to sporting event tickets, etc. Indeed, the brand drug company detailing program is big business. *IMS Health Inc. v. Ayotte*, 550 F.3d 42, 56 (C.A.1, 2008) ("The fact that the pharmaceutical industry spends over $4,000,000,000 annually on detailing bears loud witness to its efficacy.") Generic companies do not detail generic drugs. Rather, a majority of States have mandatory substitution laws, wherein a prescription for a branded drug must be filled, at the pharmacist level, with a generic version if it exists. Furthermore, generic drug companies compete usually only on price because all generic drug companies that have the underlying product necessarily means that the medicine is the same 21USC§ 355(j). Accordingly, no generic company puts out ads in magazines, buy television advertising spots, have direct-to-consumer advertising, have detailing to doctors, or give out "freebies", etc. All this effort is expected to show what the generic company does not do and agrees it won't do to market the product for the patented use.

Furthermore, a winning generic company after Para IV litigation cannot even be made whole because of the lost market opportunity whilst the patent litigation was pending (for generally at least 30-months) and that it cannot usually recover meaningful attorney fees or costs under the "American Rule." See, *Buckhannon Bd. and Care Home, Inc. v. West Virginia Dept. of Health & Human Resources*, 532 U.S. 598, 602 (2001)("In the United States, parties are ordinarily required to bear their own

attorney's fees-the prevailing party is not entitled to collect from the loser. Under this "American Rule," we follow a general practice of not awarding fees to a prevailing party absent explicit statutory authority."). In short, simply by filing an abusive lawsuit, the brand company enjoys a 30-month stay of generic competition, thereby needlessly depriving the public of a valid generic drug.[5]

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[5] See, Generic Pharmaceutical, Section 11:2; See also, *aaiPharma Inc. v. Thompson*, 296 F.3d 227, 236 (C.A.4, 2002) ("The question is important because, as we explained earlier, listing of a patent in the Orange Book triggers the availability of the thirty-month stay. If there is no enforcement mechanism to ensure that an NDA holder complies with its statutory obligations, an NDA holder can abuse the Orange Book listing process in such a way that (1) the NDA holder enjoys the protection of the thirty-month stay when it is not entitled to do so, or (2) a third party patentee (a person or entity other than the pioneer drug company that holds a patent claiming a pioneer drug) fails to recei the protection of the stay even though it is entitled to receive that protection. The first (and more serious) problem arises when an NDA holder wrongly lists a patent in the Orange Book that does not actually claim its approved drug under the standard set forth in § 355(c)(2). Once the patent is listed, the NDA holder can delay an ANDA applicant's entry into the marketplace for up to thirty months (and extend its monopoly power) simply by filing a patent infringement suit. The NDA holder receives this benefit regardless of whether the patent meets the statutory criteria for Orange Book listing. Thus, the absence of any mechanism for ensuring the accuracy of Orange Book listings means that "the patentee/NDA holder [can receive] almost automatic injunctive relief for even marginal infringement claims." Terry G. Mahn, Patenting Drug Products: Anticipating Hatch-Waxman Issues During the Claims Drafting Process, 54 Food Drug Cosm. L.J. 245, 250 (1999). The harm to generic drug manufacturers, and ultimately to the consuming public, is obvious.

II. Left Uncorrected, the divided ruling below incorrectly placed blame on the FDA that is now hampered in its ability to administer the Act

Judge Clevenger, in his concurrence, erred in blaming the FDA for gumming up the works. Novo instigated the situation, not the FDA.

Novo's exchanges with FDA. Before changing its use code, Novo asked the FDA to adopt the position that, "[a]s there will only be a single indication for PRANDIN, there is no additional indication or use that can be carved out by a section viii statement." But the FDA said no. Even though the FDA requested "a simplified indication" in the "'INDICATIONS AND USAGE section of the labels," it explained, the "DOSAGE AND ADMINISTRATION section" would "carv[e] out the metformin information," which it noted "will not render the product less safe or effective." Pet. 44a-49a & nn.17-20. In other words, the simplified indication would affect one portion of the repaglinide label; the carve-out would affect another.

It is, therefore, wrong to say, as did the majority, that the FDA "gummed up the works," "created" Caraco's problem, or "tipped the careful balance in the favor of pioneering manufacturers." 601 F.3d at 1368. The FDA did no such thing. Instead, FDA *accepted* Caraco's carve-out, and *approved* its Section viii statement. As the agency put it, "FDA has concluded when information regarding the combination use of repaglinide with metformin is carved out, generic repaglinide will remain safe and effective for the remaining, nonprotected conditions of use." It doesn't get any clearer than that. Judges Clevenger and Rader ignored this straightforward FDA decision

and declared that FDA did the opposite. 601 F.3d 1367-68.

Novo's admissions at oral argument. Judge Clevenger was also mistaken in asserting that the FDA "instructed Novo to '[s]ubmit the description of the approved indication *or* method of use that you propose FDA include as the 'Use Code' in the Orange Book," 601 F.3d at 136 (emphasis added)—as if the FDA somehow "instructed" Novo to switch from its accurate use code to the misleading one. Here again, the FDA did no such thing—which is why "Novo *admitted* that FDA did not direct or request that Novo changes its use code, nor was this required under FDA regulations." 601 F.3d at 1380 (emphasis added).

Indeed, the rest of the form (to propose the use code) shows that, contrary to Judge Clevenger's suggestion, Novo *violated* the form by changing its use code. On the prior page, the form explains that the "information" to be provided is "*[f]or each approved method of use claimed by the patent.*" Pet. 212a (emphasis added); *see also* 21 C.F.R. § 314.53(c)(2)(ii)(P)(2) (requiring Novo to identify "the specific section of the approved labeling for the drug product *that corresponds to the method of use claimed by the patent submitted.*") (emphasis added). When Novo changed its use code, it violated this instruction because Novo's new code covers uses *not* claimed by the patent. 601 F.3d at 1380. The majority erred in blaming FDA for "gumm[ing] up the works." 601 F.3d at 1368.

III. Left Uncorrected, the Majority Opinion Facilitates Gaming of the Act to Delay Generic Drug Approvals.

Though the majority erred in blaming FDA, it correctly perceived that the result here tips the Hatch-Waxman balance in favor of brands—in situations where the generic concededly does not infringe. This is indeed an "extraordinary result", which, as Judges Clevenger and Dyk recognized, cannot adequately be addressed by Paragraph IV litigation. To the contrary, the decision will open the floodgates to brand abuse of method patents and even threaten FDA's authority to implement the statute.

Brand abuse. Congress enacted the counterclaim provision precisely "to prevent manipulative practices by patent holders with respect to Orange Book listings," which "were designed to *delay* the onset of competition from generic drug manufacturers." 601 F.3d at 1368 (emphasis added). But now, under the majority's ruling, any time a brand holds a compound patent with multiple approved uses, it can block all generic competition so long as it has a patent covering a ***single*** approved use. The only question left by the majority's decision is, who will suffer next?

As noted by Judge Dyk, "[t]he manipulative nature of Novo's actions is confirmed not only by the lack of justification for the change, but also by the timing of the change (two years after the labeling change was initiated by the FDA and immediately after the FDA approved Caraco's section viii carve-out), and by its own admission that preventing approval of Caraco's ANDA was part of the motivation for changing the use code." 601 F.3d at 1381. To this, we must add Novo's admission that "FDA did not direct or request

that Novo change its use code, nor was this required under FDA regulations." 601 F.3d at 1380.[6]

It is no answer to say that FDA should not take use code descriptors at face value. 601 F.3d at 1368. *See Purepac Pharm. Co. v. Thompson*, 354 F.3d 877 (D.C. Cir. 2004) ("FDA . . . does not evaluate patent information"; it simply "publishes information it receives"). "[I]ssues of patent claim and infringement are matters of patent law, and FDA does not have the authority . . . to assess whether a submitted patent claims an approved drug and whether a claim of patent infringement could reasonably be made against an unauthorized use of the patented drug." Testimony of Lester M. Crawford, Dep. Comm'r of Food & Drugs, House Committee on Energy &

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[6] Many drugs are also combined with other drugs to form combination drugs, eg., cough + sinus combination product. A patent expiring on the "cough" medicine ought to allow generic companies to make and sell a generic cough medicine. But if the brand company has a combination patent (to the cough + sinus combination) and submits a Use Code that states, "use of cough medicine to treat cold and flu symptoms" then in effect, the expiring cough medicine patent cannot be practiced because the generic company would be forced to include the full Use Code description, which could colorably include the use in combination with sinus medicine, and hence possibly infringing the combination patent. Thus, one cannot ever practice the so-called monotherapy using cough medicine alone even though the relevant patent is now expired. This court has reaffirmed that subject matter claimed in an expired patent is dedicated to the public, and remains free for the public to use. *Bonito Boats v. Thundercraft Boats*, 489 U.S. 141,152 (1989). The Founders and this Court understood that the presumption is that all technology is fair-game for the public to freely exploit subject to patent protection existing. *Bonito Boats*, 489 U.S. at 146-147. Accordingly, this Court should construe close-calls in favor of free-exploitation.

Commerce, Oct. 9, 2002. After all, the Hatch-Waxman Act requires the FDA to "*publish*" patent information—not to evaluate it. 21 U.S.C. § 355(c)(2) (emphasis added). FDA simply does not possess the expertise to evaluate patents.[7] Nor does FDA have the resources to do so.

FDA is now deprived of authority to require use codes. The majority opinion also extinguishes FDA's authority to require use codes. "According to the majority, method of use information is not 'patent information.' The majority construes the term as limited to the patent number and expiration date: '[T]he Act defined the term 'patent information' as 'the patent number and expiration date.'" 601 F.3d at 1370-71. FDA's settled reading of the term (and Congressional adoption too) require patent descriptions. But it also means the FDA has no authority to require use codes in the first place, which leaves FDA without its well-established tool to implement Section viii. Congress could not have intended this result.

Finally the panel decision emphasized certain parts of the statute, but judicially eviscerated other parts of the same statute. The panel emphasized the portions relating to "patent" and "expiration":

> If *the patent information described in subsection (b)* of this section could not be filed with the submission of an application under subsection (b) of this section ..., the holder of an approved application shall file with the Secretary *the patent num-*

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[7] *Watson Pharmaceuticals, Inc. v. Henney*, 194 F.Supp.2d 442, 445-446 (D.Md. 2001) ("In this case, it is paramount to keep in mind that the FDA, in deciding to make an Orange Book listing, is not acting as a patent tribunal. It has no expertise-much less any statutory franchise-to determine matters of substantive patent law.").

> *ber* and *the expiration date* of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. [601 F.3d at 1361]

But the panel ignored the rest, rendering the following language superfluous:

> If *the patent information described in subsection (b)* of this section could not be filed with the submission of an application under subsection (b) of this section ..., the holder of an approved application shall file with the Secretary *the patent number* and *the expiration date* of any patent ~~which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.~~

IV. Proper Use of Section viii Has Resulted in Successful Generic Drug Launches Saving Billions for Patients

When the compound patent expired protecting King Pharma's blockbuster drug, Altace® (generic – ramipril), indicated for cardiac treatment, generic companies successfully launched because generic companies used Section viii statements to carve out those other patented uses. Altace® had 2006 brand sales of over $650 million. Pravachol's® (generic – pravastatin) sole remaining patent in the Orange

Book relates to a method of use patent. Pravachol® was a blockbuster cardiac statin that went generic in 2006 and recorded 2004 sales of over $2.6 billion. With generic drugs, patients benefit because insurance co-pays are dramatically reduced. For example, a particular insurance plan may charge the patient a $25 co-pay for branded drugs whereas only charge $5 co-pay for generic drugs. In this regard, a switch to generic drugs saves the patient $20 – this savings could be used to purchase another 4 generic drugs thereby increasing overall patient health.

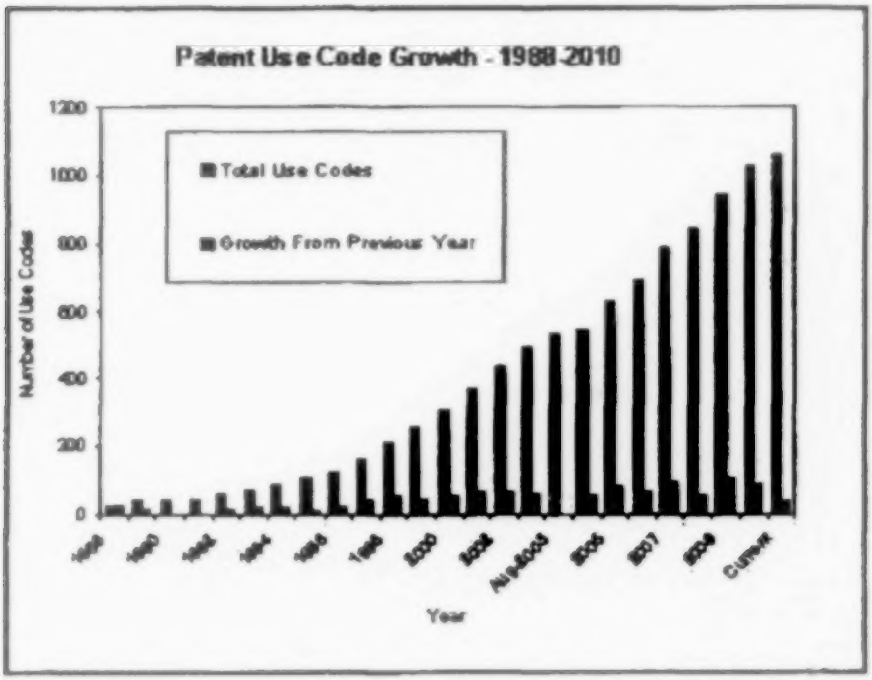
This issue is now percolating in the Crestor® (generic – rosuvastatin) litigation, wherein the brand company alleges that the Section viii is inappropriate and cheats the brand company of its day in court. See, *Astrazeneca Pharmaceuticals LP v. Apotex Corp.*, 2010 WL 5376310, at *13 -14 (D. Del., 2010) ("Plaintiffs next argue that Section 271(e)(2) will be rendered meaningless if generic manufacturers can evade suit under Section 271(e)(2) by simply filing a conclusory section viii statement that they are not seeking approval for any patented indications. According to Plaintiffs, "[s]uch an approach would improperly and unfairly allow generic companies to define and dictate the circumstances under which the filing of an ANDA would constitute infringement under § 271(e)(2)." (Pl. Opp. Br. at 19). This argument is also misguided, and the Federal Circuit rejected it in Warner-Lambert. See Warner-Lambert, 316 F.3d at 1360. The formality of submitting a section viii statement does not immunize a generic manufacturer from suit under Section 271(e)(2).").

A recent investment banking research report even laid out the pathway for the brand company to play the use code game to protect Crestor®:

> File section viii seeking a restricted label to avoid infringing both the '152 and '618 Orange Book patents. AZN (AstraZeneca) will likely respond with (i) filing a Citizens Petition (ii) Argue that its PUC (patent use code) code prevents a carve out approval. Risk assessment – we anticipate a 90% probability that the FDA is unable to carve out an indication for the ANDA.

Source: Morgan Stanley Research Europe, 01 Sept. 2010, Pharmaceuticals Report, entitled, "Potential Selective Upside for Industry post Prandin Ruling," at page 6.

The Morgan Stanley report also shows the rapid growth of use codes.



CONCLUSION

This Court's intervention is urgently needed to prevent that "extraordinary result" of gamesmanship of the use code system and evisceration of the Section viii program. The petition for a writ of certiorari should be granted.

Respectfully submitted,

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January, 2011

AMICUS CURIAE BRIEF

No. 10-844

In The
Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD. AND SUN PHARMACEUTICAL INDUSTRIES, LTD.,

Petitioners,

v.

NOVO NORDISK A/S AND NOVO NORDISK, INC.,

Respondents.

On Petition For A Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

BRIEF FOR CONSUMER FEDERATION OF AMERICA AND U.S. PIRG AS AMICI CURIAE IN SUPPORT OF PETITIONERS' PETITION FOR CERTIORARI

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INTERESTS OF AMICI CURIAE[1]

Amici Curiae Consumer Federation of America and U.S. PIRG are leading advocates for competitive and transparent pharmaceutical markets, including generic pharmaceuticals' access to markets, which benefit all consumers by maintaining lower prices, promoting innovation, and developing efficiencies. These goals would be significantly compromised if brand pharmaceuticals are further encouraged to circumvent the unambiguous text, structure, and purpose of the Hatch-Waxman Act by manipulating patent use codes without allowing injured generic pharmaceutical companies the opportunity to assert relevant counterclaims.

The Consumer Federation of America (CFA) is composed of over 280 state and local affiliates representing consumer, senior-citizens, low-income, labor, farm, public power, and cooperative organizations. CFA represents consumer interests before federal and state regulatory and legislative agencies, participates in court proceedings as amicus curiae, and conducts research and public education.

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[1] The parties were timely informed of the intent to file the amici brief. The parties have consented to the filing of this brief, and the parties' letters of consent to the filing of this brief are on file with the Clerk. Pursuant to Rule 37.6, amici curiae state that no counsel for a party wrote this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person or entity, other than the amici curiae, its members, or its counsel, has made a monetary contribution to this brief's preparation or submission.

U.S. PIRG, the federation of state Public Interest Research Groups (PIRGs) is a not for profit consumer advocacy organization that stands up to powerful special interests on behalf of the American public. With a strong network of researchers, advocates, organizers and students across the country, it takes on the special interests when they stand in the way of reform and progress.

INTRODUCTION AND SUMMARY OF ARGUMENT

This Court's review is urgently needed to prevent the decision below from greatly increasing the cost of generic drugs for ordinary Americans. The Hatch-Waxman has saved American consumers, including members of the amici curiae, literally hundreds of billions of dollars in unnecessary expenses for needed medicine. The decision below threatens to take a large bite out of those savings, and is contrary to Congress' intent and the plain text and structure of the Act.

Congress updated the Medicare Prescription Drug Improvement and Modernization Act (collectively, the "Hatch-Waxman Act") in 2003 to ensure the effectiveness of the Act's streamlined procedure for a generic product to reach the market when its use is different from the use patented by the brand manufacturer. Under what is known as "section viii" of the Act, the generic manufacturer files an abbreviated new drug

application (ANDA) demonstrating a permitted use of a patented product. This procedure contains a mechanism to safeguard the patent holder by allowing the patent holder to pursue an injunction within forty-five days of the ANDA filing. At the same time, to ensure that the patent-holding brand manufacturer does not abuse its position by merely enjoining any ANDA filed, Congress in 2003 passed a counterclaim provision that provides generic pharmaceutical manufacturers with a method for challenging brand actions.

It was Congress' intent to balance the interests of brand and generic manufacturers in an effort to promote innovation and facilitate consumer access to affordable medicine. For instance, to allow for future consumer benefits, Congress and the FDA have acted to ensure that brand manufacturers whose "method" patents cover only specific uses of a drug do not expand those patents beyond their lawful bounds. Thus, if a given pharmaceutical is proven useful for a non-patented use, it is Congress' will that this drug reach the consumers through generic manufacturing without having to wait for the expiration of yet another patent.

The gamesmanship employed by Novo/Nordisk when it changed its patent use code – admittedly incorrectly – in response to Caraco's ANDA filing is a brazen abuse of the Hatch-Waxman Act, FDA regulations, and the intent of legislators and policymakers. Congress was aware that the complexities of FDA pharmaceutical approval lend themselves to creative

manipulations, and provided generics with the opportunity to counteract such strategies through the counterclaim provision. The counterclaim provision is wide-reaching, both because "section viii" ANDA applications are so common and because the provision is designed to allow generics to combat a wide array of deceptive tactics. Blocking a brand manufacturer from a post-hoc, incorrect change to its patent use code certainly falls within the scope of intended counterclaims.

The harm to consumers from this action is both immediate and far-reaching. Immediately consumers face one fewer generic on the market that they should otherwise have access to. This action also opens the door for other brands to employ similar tactics, thereby effectively ending any hope that a non-patented use will ever reach consumers through generics, as intended. Furthermore, this rewards and encourages brand manufacturers to continue to devise new ways to circumvent the rules, and virtually ensures consumers will continue to suffer the effects of limited access to the medicine they need.

Review is needed now to prevent these unfortunate results of the Federal Circuit's fractured ruling.

ARGUMENT

I. THE FEDERAL CIRCUIT THREATENS THE VIABILITY OF MECHANISMS VITAL TO GENERIC COMPETITION AND THEREFORE CONSUMER ACCESS TO GENERIC PRODUCTS

Consumer access to generic pharmaceuticals is a key initiative for both Congress and regulatory agencies. Representative Waxman summarized the Congressional approach to generics during his 2009 testimony, explaining:

> Generic drugs play a crucial role in promoting public health where they are available. They promote competition, which in turn lowers prices. Lowering drug prices reduces overall health care bills. More importantly though, lower drug prices means access to important medications for many patients who might not otherwise be able to afford them. Today in the U.S. a remarkable 67% of prescriptions are filled with generic medicines, saving consumers and the federal and state governments tens of billions of dollar annually.[2]

As the Department of Health & Human Services recently observed "[d]ramatic growth in the use of generic drugs has generated substantial savings for

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[2] *Protecting Consumer Access to Generic Drugs Act of 2009: Hearing on H.R. 1706 Before the H. Subcomm. on Com., Trade and Consumer Protection, H. Comm. on Energy and Com.*, 111th Cong. 11 (2009) (statement of Rep. Henry Waxman, Chairman, House Comm. on Energy and Comm.).

American consumers." *ASPE Issue Brief: Office of the Assistant Secretary for Planning and Evaluation, Office of Science and Data Policy – U.S. Department of Health and Human Services, Expanding the Use of Generic Drugs* at 2 (Dec. 1, 2010). Indeed, generic products have saved American consumers over $824 billion over the past decade and almost $140 billion in 2009 alone.[3] Clearly this is an important program for consumers, as access to generics is becoming a virtual necessity for those that cannot afford brand name pharmaceuticals.

The Hatch-Waxman Act and the counterclaim provision in particular both serve as integral defenses for the generic pharmaceutical industry. Removing the teeth from the counterclaim provision invites brand name pharmaceutical manufacturers to sue each and every generic product that appears, obtaining the benefit of an automatic 30-month stay of FDA approval of generic marketing. This litigation, whether successful or not, delays market entry by years and raises the cost of business for generics to the point where entry may no longer be an option. Like other tactics that garner more of the headlines, blocking

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[3] Press Release, Generic Pharmaceutical Association, Generic Medicines Saved U.S. Health Care System $139.6 Billion in 2009; $824 Billion Saved over the Last Decade (July 26, 2010), *available at* http://www.gphaonline.org/sites/default/files/July%2026%20National_Savings_Study_Press_Release.pdf.

generics through patent use code manipulation is substantially capable of derailing an entire initiative.[4]

Simply put, the counterclaim provision is vital to enabling generics to follow the path laid out in "section viii" of the Act. There are numerous examples of instances in which section viii generics have succeeded and saved consumers a considerable amount of money. For instance, Kremers Urban Development Company, operating as Schwartz Pharma, succeeded in obtaining section viii approval for a generic version of the heartburn medicine Prilosec in November of 2002.[5] Consumers enjoyed access to critical medicine while Schwarz Pharma experienced a 55% growth in sales in the following year.[6] This is a two-fold benefit to consumers. First, the specific drug in question is available at a more affordable price. Second, another competitor is able to gain traction in an otherwise consolidated pharmaceutical market. Without section

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[4] *Protecting Consumer Access to Generic Drugs Act of 2007: Hearing on H.R. 1902 Before the H. Subcomm. on Com., Trade and Consumer Protection, H. Comm. on Energy and Com.*, 110th Cong. 9 (2007) (Oral Statement of Jon Leibowitz, FTC Commissioner), *available at* http://www.ftc.gov/speeches/leibowitz/070502reversepayments.pdf.

[5] U.S. Food and Drug Administration Center for Drug Evaluation and Research, Approval Package for Application Number 75-410, November 1, 2002, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/075410.pdf.

[6] L.J. Sellers, *Pharm. Exec. 50*, PHARMACEUTICAL EXECUTIVE, May 2004, at 4, *available at* http://pharmexec.findpharma.com/pharmexec/data/articlestandard//pharmexec/202004/95192/article.pdf.

viii as a viable means for obtaining FDA approval, AstraZeneca would still be able to demand exorbitant prices for brand Prilosec, and Schwartz Pharma would still be a relatively obsolete competitor.

Without a functioning and employable counterclaim option, generics will continue to experience difficulties in marketing their drugs for non-patented uses. This will lead to fewer attempts to market and, ultimately, the erosion of the entire industry. Frustratingly, this scenario was foreseen. The counterclaim is merely a tool to prevent the brands from preventing the generics to pursue their legally available avenue. It is not as though the counterclaim provision avails generics to a path for dismantling the brand manufacturers. It is merely an opportunity to correct abuses by the brands.

This Court's review is needed to prevent the counterclaim provision from being eviscerated, to the ultimate detriment of consumers.

II. THE FEDERAL CIRCUIT'S OPINION REWARDS AND ENCOURAGES CONTINUED GAMESMANSHIP AND MANIPULATION BY BRAND MANUFACTURERS

Federal courts have acknowledged that the FDA lacks the resources to closely monitor compliance with Orange Book, and as a result misrepresentation and fraud is commonplace. For instance, one court explained, "we have no reason to believe that because applicants are *supposed* to submit information about

approved uses only, they *in fact* do so." *Purepac Pharm. Co. v. TorPharm, Inc.*, 354 F.3d 877, 884 (D.C. Cir. 2004). In explaining, the court upheld the district court's analysis that an agency's practical inability to conduct patent review "creates the possibility for conflict between NDA holders and ANDA applicants over the proper scope of a particular use patent." *Purepac Pharm. Co. v. Thompson*, 238 F. Supp. 2d 191, 205 (D.D.C. 2002). The courts agree with the consumer groups in this analysis: left unchecked, brand pharmaceutical companies will exploit regulatory procedural loopholes, including the misrepresentation of required information.

Brand manufacturing companies will be aware that they have freedom to engage in fraud during Orange Book filings. The law requires the brand manufacturer to include its method-of-use patent for its Orange Book filing. 21 C.F.R. §314.53(c)(2)(ii)(P)(2). The method-of-use patent description should be precise to provide notice to generics regarding potential opportunities for carve outs.[7]

However, with judicially sanctioned lack of oversight, brand name pharmaceutical companies are likely to begin obtaining use codes for extremely broad methods-of-use. As one commentator notes,[8]

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[7] FDA Approval to Market a New Drug: Patent Submission and Listing Requirements, 68 Fed. Reg. 36,676, at 36,683 (2003).

[8] Julie Dohm, *Expanding the Scope of the Hatch-Waxman Act's Patent Carve-Out Exception to the Identical Drug Labeling*

(Continued on following page)

and the facts here confirm, brand manufacturers have already begun employing this strategy.[9] If the Court allows the panel's decision to stand, it will not be long until we start seeing highly generalized Orange Book use codes such as "treatment for cancer," thereby eliminating any possibility of entry for all generic manufacturers.

Judge Gajarsa's dissent acknowledged this fact. He explained, "With the majority's blessing, pioneering drug manufacturers now have every incentive to follow Novo's lead and draft exceedingly broad use codes thereby insulating themselves from generic competition and rendering Section viii a dead letter." *Novo Nordisk A/S & Novo Nordisk v. Caraco Pharm. Labs., Ltd.*, 615 F.3d 1374, 1377 (Fed. Cir. 2010) (Gajarsa, J., dissenting).

This does not even take into account the broader effect that such a ruling has on the pharmaceutical industry. By granting brand manufacturers this allowance for deceitfulness and gamesmanship, we are opening the door to future litigation over deceptive or manipulative practices.

Requirement: Closing the Patent Litigation Loophole, 156 U. PA. L. REV. 151, 162-63 (2007).

[9] For instance, the FDA assigned a use code for the "treatment of neurodegenerative diseases." See Ctr. for Drug Evaluation & Research (CDER), FDA, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations (2007), *available at* http://www.fda.gov/cder/orange/obannual.pdf.

Nor will the panel's suggestion that Paragraph IV litigation serves as a satisfactory constraint on brand manufacturers' exploitation prove true. First, Congress has authorized the FDA – not the federal courts – to assess the potential health and safety risks of proposed drug labeling. To depend on Paragraph IV litigation would risk leaving health and safety concerns regarding the generic drug without review. Second, Paragraph IV litigation is impractical. Brand manufacturers could engage in litigation strategies to raise the costs of generics, and ultimately make the prospect of entry unprofitable. Both Judges Clevenger and Dyk acknowledge that Paragraph IV litigation is unlikely to satisfactorily resolve these issues. Conc. Op. 1 ("I am not as certain as Judge Rader that the ongoing Paragraph IV litigation will cleanly resolve the dispute between the parties."); Dissent 26 ("[T]he concurrence doubts that there is a remedy in the infringement suit, and I agree."). *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 601 F.3d 1359, 1381 (Fed. Cir. 2010) (Dyk, J., dissenting).

III. THE FEDERAL CIRCUIT'S NARROW INTERPRETATION OF THE COUNTERCLAIM PROVISION OF THE HATCH-WAXMAN ACT CIRCUMVENTS THE CLEAR LEGISLATIVE INTENT

Congress' intent when enacting the Medicare Prescription Drug, Improvement, and Modernization

Act of 2003[10] was clear. Senator Schumer best summarized the purpose of the bill, emphasizing that:

> [t]he provisions *close loopholes* in the law and *end the abusive practices* in the pharmaceutical industry which have kept lower-priced generics off the market and cost consumers billions of dollars. . . . [T]he provisions enforce the patent listing requirements at the FDA by allowing a generic applicant, when it has been sued for patent infringement, to file a counterclaim to have the brand drug company delist the patent or correct the patent information in FDA's Orange Book.[11]

As indicated by this statement, Congress identified brand manufacturers and generics as competing interests, recognized the abusive and deceptive tactics employed by brand manufacturers, and designed a counterclaim provision as a direct and immediate remedy to these tactics.

The Federal Circuit's ruling has the effect of disassociating the patent use code narrative from the essential features of the patent, such as the patent number and expiration date. However, the Food, Drug, and Cosmetic Act[12] refers to "patent information"[13] by

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[10] Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, §1101(a)(2)(C), 117 Stat. 2066, 2452 (codified at 21 U.S.C. §355(j)(5)(C)(ii)).

[11] 149 Cong. Rec. 31200 (Nov. 23, 2003) (statement of Sen. Schumer) (emphasis added).

[12] 21 U.S.C. §301 et seq.

[13] 21 U.S.C. §355(b).

incorporating the patent number and expiration date in combination with "method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."[14] As such, this bifurcation of what constitutes a patent under the counterclaim provision is incongruous with how the very statute identifies "patent information." This court has consistently held that, when interpreting a statute, it "must not be guided by a single sentence or member of a sentence, but look to the provisions of the whole law, and to its object and policy." *Mastro Plastics Corp. v. NLRB*, 350 U.S. 270, 285 (1955) (quoting *United States v. Boisdo's Heirs*, 49 U.S. 113, 122 (1850)). The divided ruling below contravenes these principles, at the expenses of those who need timely access to low-cost generic drugs.

As recently as 2009, Chairman Henry Waxman – one of the authors of the bill in question – opined that the Hatch-Waxman Act is being misused to accomplish the opposite of its intended goal. Representative Waxman stated "[T]his is the last thing Congress intended when we enacted Waxman-Hatch. The law was intended to give consumers access to generics at the earliest possible opportunity, not to line the pockets of generic and brand-name drug companies."[15]

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[14] *Id.*

[15] *Protecting Consumer Access to Generic Drugs Act of 2009: Hearing on H.R. 1706 Before the H. Subcomm. on Comm., Trade and Consumer Protection, H. Com. on Energy and Com.*, 111th

(Continued on following page)

The rationale behind the amendments is clear. The Hatch-Waxman Act provides ample incentives for brand manufacturers to develop innovative drugs. However, the brand manufacturers expanded the scope and duration of these patents through numerous channels, always to the detriment of generic manufacturers and, ultimately, consumers. Abusive filings in the Orange Book are a particularly fruitful avenue of abuse, according to the FTC. The FDA does not police the Orange Book, nor does it seek out sham filings. Rather, its role is "solely ministerial."[15] The counterclaim provision presents the generics with their only realistic opportunity to combat systematic abuses of this ministerial system.

Just as he acknowledged the ultimate effect this ruling would have on section viii and generic access to a path of entry, Judge Gajarsa also recognized that the Federal Circuit's ruling was in complete abrogation of Congress' intent, explaining "the majority decision likely leaves generic manufacturers such as Caraco with no other remedy . . . Caraco also cannot disprove infringement in the infringement lawsuit . . . [t]his is an untenable and absurd result, and contravenes the intent of Congress in adopting the counterclaim provision." *Novo Nordisk A/S*, 615 F.3d at 1378 (Gajarsa, J., dissenting).

Cong. 12 (2009) (statement of Rep. Henry Waxman, Chairman, House Comm. on Energy and Comm.).

[15] Fed. Trade Comm'n, *Generic Drug Entry Prior to Patent Expiration: An FTC Study*, i (July 2002), available at http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf.

Review of the divided ruling below is needed to prevent the very consequences that Congress specifically sought to prevent.

Certiorari is therefore warranted.

CONCLUSION

Because of the clear disregard for legislative intent, the immediate harm to consumers who should have access to generic drugs, and the pervasive effect the Federal Circuit's ruling will have on the generic pharmaceutical industry, the petition for a writ of certiorari should be granted.

Respectfully submitted,

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AMICUS CURIAE BRIEF

No. 10-844

In the Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD. AND SUN PHARMACEUTICAL INDUSTRIES, LTD.,

Petitioners,

v.

NOVO NORDISK A/S AND NOVO NORDISK, INC.,

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF FOR THE GENERIC PHARMACEUTICAL ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

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BRIEF FOR THE GENERIC PHARMACEUTICAL ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

INTEREST OF *AMICUS CURIAE*[1]

The Generic Pharmaceutical Association (GPhA) is a nonprofit, voluntary association representing more than 100 manufacturers and distributors of finished generic pharmaceutical products, manufacturers and distributors of bulk active pharmaceutical chemicals, and suppliers of other goods and services to the generic pharmaceutical industry. GPhA's members provide American consumers with safe, effective, and affordable generic drugs. Their products account for nearly 75% of all prescriptions dispensed in the United States, and they save consumers more than $120 billion each year.

GPhA's core mission is to improve the lives of consumers by providing timely access to affordable pharmaceuticals. The decision below undermines that goal by enabling brand-name manufacturers to block generic entry through the submission of erroneous patent information to the Food and Drug Administration (FDA). GPhA respectfully submits

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[1] No counsel for a party authored this brief, in whole or in part, and no counsel for a party or party made a monetary contribution intended to fund the preparation or submission of this brief. No person or entity other than *amicus curiae* or its counsel made a monetary contribution to this brief's preparation or submission. Petitioners and respondents received timely notice of *amicus*'s intent to file this brief and have consented to its filing; their written consents have been submitted to the Clerk.

this *amicus curiae* brief to address the adverse ramifications of the court of appeals' decision and the urgent need for this Court's review.

STATEMENT

1. Congress passed the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act), Pub. L. No. 98-417, 98 Stat. 1585, with the primary objective of "mak[ing] available more low cost generic drugs." H.R. Rep. No. 98-857, pt. 1, at 14 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2647. The Act furthers that objective through two principal mechanisms that allow generic versions of brand-name drugs to be "marketed more cheaply and quickly." *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661, 676 (1990).

First, the Act permits a generic manufacturer to forgo the filing of a full-fledged new drug application (NDA), see 21 U.S.C. § 355(b), and instead to file an abbreviated new drug application (ANDA), see 21 U.S.C. § 355(j). If the generic applicant demonstrates that its generic version is bioequivalent to the brand-name drug, the ANDA may rely on the clinical safety and efficacy data submitted by the brand-name manufacturer with its NDA, thus eliminating costly and time-consuming duplication of clinical studies. See *Eli Lilly*, 496 U.S. at 676; *Merck KGaA* v. *Integra Lifesciences I, Ltd.*, 545 U.S. 193, 196 n.1 (2005) (citing 21 U.S.C. § 355(j)(2)(A)(ii), (iv), and (8)(B)).

Second, the Act seeks to expedite the resolution of disputes over the validity and scope of patents that the brand-name manufacturer claims protect its

product. The Act does so by requiring an NDA applicant to

> file with the [NDA] the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the [NDA] or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.

21 U.S.C. § 355(b)(1). FDA regulations in turn specify a more exhaustive list of "patent information" that must also be submitted with the NDA. 21 C.F.R. § 314.53(c)(1)-(2). Once an NDA is approved, the drug is listed along with its associated patent information in the FDA publication, *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the Orange Book. See 21 U.S.C. § 355(j)(7)(A)(i)(I) and (ii).

An ANDA must contain a response to each patent listed in the Orange Book for the brand-name drug that the ANDA references. With respect to each such patent, the applicant generally must make one of four certifications: (I) the required patent information has not been filed with FDA; (II) the patent has expired; (III) the patent will expire on a specified date; or (IV) the patent is invalid or will not be infringed by the manufacture, use, or sale of the generic drug for which approval is sought. 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV).

2. Some patents—known as "method of use" patents—apply not to the drug itself but to the manner in which the FDA has authorized the drug to be used. For example, a brand-name manufacturer may hold a patent on using Drug X, in combination with Drugs Y and Z, to treat a particular disease. And some approved methods of using the drug—for example, combining that same Drug X with Drugs A and B to treat a different disease—may not be patented.

The rules are slightly different with respect to such patents. If a method-of-use patent claims at least one but fewer than all of the approved methods, then the ANDA applicant, instead of making one of the certifications described above, may also choose to "carve out" the patented uses of the drug with a "section viii" statement. A section viii statement means that the generic applicant does not seek FDA approval for the patented uses. In that case, the ANDA must contain a statement that the relevant patent "does not claim a use for which the applicant is seeking approval." 21 U.S.C. § 355(j)(2)(A)(viii).

3. Although both a paragraph IV certification and a section viii statement may permit an ANDA applicant to obtain FDA approval before expiration of a patent listed by the brand-name manufacturer in the Orange Book, the two options have very different implications for the timing of FDA approval. A paragraph IV certification will significantly delay approval in many cases. The filing of a paragraph IV certification is an act of patent infringement, see 35 U.S.C. § 271(e)(2)(A), subjecting the ANDA applicant to suit by the brand-

name manufacturer. If the brand-name manufacturer files a patent infringement suit within 45 days after receiving notice of the ANDA applicant's certification, the FDA's approval of the ANDA is automatically stayed for 30 months, unless a court determines before that time that the patent is invalid or would not be infringed by the marketing of the generic drug. 21 U.S.C. § 355(j)(5)(B)(iii). A section viii statement, by contrast, does not delay FDA approval, see 21 U.S.C. § 355(j)(5)(B)(i)-(iii), because it asserts that the patent as described in the Orange Book does not even claim to cover the use in question.[2]

4. This case arises from petitioners' application to the FDA for approval to market a generic version of repaglinide, a diabetes drug manufactured by respondents under the brand name PRANDIN. The application sought to market generic repaglinide for two uses that respondents concede did not violate their patents on the drug. Nevertheless, respondents sought to block petitioners' application by amending the description of a patent on file with the FDA to claim (erroneously) that the patent in fact covers petitioners' proposed use. As a result, the FDA rejected petitioners' request for approval of a label that would omit reference to the patented method for using repaglinide, thereby disabling petitioners from

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[2] Paragraph I and paragraph II certifications likewise do not delay approval of the ANDA because they are premised on the non-existence of an applicable patent. See 21 U.S.C. § 355(j)(5)(B)(i). A paragraph III certification delays final FDA approval until the patent's expiration date. See 21 U.S.C. § 355(j)(5)(B)(ii).

arguing that the generic version they sought to distribute would not infringe respondents' patent.

Respondents brought this patent infringement action against petitioners for proposing to market a generic version of repaglinide. Petitioners filed a counterclaim under 21 U.S.C. § 355(j)(5)(C)(ii)(I), which authorizes defendants in an infringement action to bring a "counterclaim seeking an order requiring the [patent] holder to correct or delete the patent information submitted by the holder * * * on the ground that the patent does not claim * * * an approved method of using the drug." 21 U.S.C. § 355(j)(5)(C)(ii)(I). A sharply divided panel of the Federal Circuit held that such a counterclaim is available only when the patent at issue does not claim *any* approved method of using the drug. That is, so long as the brand-name manufacturer's method-of-use patent covers at least one approved use, a generic manufacturer cannot file a counterclaim to dispute an erroneous description that blocks the generic's application.

SUMMARY OF ARGUMENT

The Federal Circuit's decision in this case incorrectly resolves an important issue of federal law and will have serious adverse consequences for generic drug manufacturers, the FDA, and American consumers. This Court's immediate review is warranted.

A. As a general matter, brand-name manufacturers have long sought to block or delay generic competition through manipulation of the Hatch-Waxman Act's patent listing procedures. Because

generic drugs are so much less expensive than their brand-name counterparts, generic entry almost immediately results in a large decrease in the brand-name incumbent's market share. Brand-name manufacturers therefore have powerful incentives to delay generic entry for as long as possible. They can accomplish that goal by overstating the scope of their patents or by filing patents of dubious validity or applicability, which will in many cases induce the generic manufacturer to file a paragraph IV certification and permit the brand-name manufacturer to obtain a 30-month stay of FDA approval. The FDA can do little to address this problem, because it lacks the authority and expertise to engage in substantive review of brand-name manufacturers' patent submissions.

B. The decision below enables—and thus encourages—brand-name manufacturers to engage in abusive manipulation of the statutory scheme. When the manufacturer of a brand-name drug holds a patent that covers at least one but fewer than all of the approved methods for using that drug, a generic manufacturer will often file a section viii statement that seeks approval to market a generic version for only the unpatented uses. See 21 U.S.C. § 355(j)(2)(A)(viii). In order to avoid infringing the brand-name manufacturer's patent, the generic manufacturer will then seek FDA approval for labeling that "carves out" the patented uses of the drug, a departure from the otherwise-applicable requirement that the generic drug bear the same label as the brand-name version.

In deciding whether to approve the carve-out label, however, the FDA defers entirely to the description of the brand-name manufacturer's patent filed with the NDA. If, as in this case, the brand-name manufacturer submits an overbroad description that covers both patented and unpatented uses, the FDA will reject the proposed labeling. The generic manufacturer will thus be required to abandon its product or go to market with a label that references the patented use and therefore infringes the brand-name manufacturer's patent.

Congress enacted a solution to this problem in Section 355(j)(5)(C)(ii)(I). That provision allows a generic manufacturer to file a counterclaim in an infringement action seeking an order requiring "correct[ion]" of the patent information submitted by a brand-name manufacturer when there is "an approved method of using the drug" that the "patent does not claim." 21 U.S.C. § 355(j)(5)(C)(ii)(I). The panel majority's erroneous conclusion that the counterclaim is available only when the patent at issue does not claim *any* approved use of the drug removes any check on the submission of overbroad patent descriptions to the FDA. Emboldened by the knowledge that their patent descriptions will not be rejected by the FDA and are not subject to judicial review, brand-name manufacturers can be expected to submit ever broader patent descriptions that bear little resemblance to the specific methods of use actually claimed by their patents. Indeed, in a recent report directed to investors in the brand-name drug industry, a major investment services firm

enthusiastically predicted that brand-name manufacturers will successfully use this strategy to block generic competition and prolong their monopoly profits.

C. The decision below also frustrates the FDA's administration of the Hatch-Waxman Act. The panel majority construed the phrase "patent information" in Section 355(j)(5)(C)(ii)(I) to mean only the number and expiration date of a patent listed by the brand-name manufacturer with the FDA. That conclusion gives no deference to 21 C.F.R. § 314.53, the FDA regulation requiring brand-name manufacturers to submit a considerably more exhaustive set of "patent information." Even though the FDA was not a party to this proceeding, the decision below still poses grave practical problems for the FDA. Because the FDA lacks the authority and expertise to evaluate the substance of brand-name manufacturers' patent listings, judicial review provides the only real check on their submission of erroneous patent information. By removing that check, the decision below converts the FDA's patent listing process into a conduit for misinformation.

D. The result of all this is to deny consumers the benefits of safe, effective, and affordable generic pharmaceuticals. Each year, generic drugs save American consumers more than $120 billion, and the cost to consumers of just a single year's delay in generic entry for a widely prescribed drug can approach $1 billion. The decision below provides brand-name manufacturers with a roadmap for blocking generic competition, and thus threatens to impose staggering costs on consumers.

ARGUMENT

A sharply divided panel of the Federal Circuit held in this case that 21 U.S.C. § 355(j)(5)(C)(ii)(I) does not permit correction of the description of a patent submitted to the FDA by a brand-name manufacturer unless the patent at issue does not claim *any* approved use of the drug. That erroneous conclusion provides brand-name manufacturers with a roadmap for blocking FDA approval of generic drugs that would not infringe any patent held by the brand-name manufacturer. As a result, the decision below will lead to serious adverse consequences for generic drug manufacturers, the FDA, and American consumers. This Court's immediate review is warranted.

A. Brand-Name Manufacturers Have Strong Incentives And Ready Means To Delay Generic Competition

As explained above, see pp. 3-4, *supra*, a generic manufacturer seeking FDA approval for a generic version of a drug must respond, patent by patent, to the listings of patents the brand-name manufacturer has previously furnished to the FDA for listing in the Orange Book. The generic manufacturer's responses govern the timing of FDA approval for its proposed generic version. If the generic manufacturer must submit a paragraph IV certification that the brand-name manufacturer's patent is invalid or will not be infringed by the generic version, then the brand-name manufacturer may initiate patent infringement litigation and obtain an automatic 30-month stay of FDA approval. See 35 U.S.C.

§ 271(e)(2)(A); 21 U.S.C. § 355(j)(5)(B)(iii). But if the generic manufacturer is able to respond that the patents as described in the Orange Book do not purport to cover its proposed generic version—either because the relevant patents have expired or because the generic manufacturer has filed a section viii statement and seeks to market the drug for only unpatented uses—then there is no delay of FDA approval. See 21 U.S.C. § 355(j)(5)(B)(i)-(iii).

Brand-name manufacturers therefore have powerful incentives to claim that a patent *does* cover a particular use of a drug. By overstating the scope of their patents or by filing patents of dubious validity or applicability, brand-name manufacturers can force ANDA applicants to make paragraph IV certifications that will stall their applications during the 30-month stay period. See Stacey L. Dogan & Mark A. Lemley, *Antitrust Law and Regulatory Gaming*, 87 Tex. L. Rev. 685, 715 (2009) (observing that brand-name manufacturers have "exploit[ed] the product-approval process" and "convert[ed] it into a tool for suppressing competition").

The potential gains to brand-name manufacturers from such manipulative conduct are dramatic. Once generic manufacturers obtain FDA approval to sell a given drug, generic products can be expected to "quickly gain a large share of the market." Cong. Budget Office, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry* 28 (1998).[3] Indeed, a study prepared by the Congressional Budget Office

[3] Available at http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf.

determined that, within a year of entering a market, generic drugs accounted for an average of 44% of prescriptions dispensed through pharmacies. *Ibid.* For seven of the drugs examined in the study, the generic manufacturers' share of the market was 65% or more within two years. *Ibid.* These figures confirm the common-sense fact that generic entry results in an immediate and dramatic decrease in sales for the incumbent brand-name manufacturer. Brand-name manufacturers therefore have every incentive to delay generic entry for as long as possible—time is money.

Meanwhile, the FDA can do little to stem the problem, because it does not review or analyze the patent information submitted to it and will not correct information in the Orange Book unless the brand-name manufacturer withdraws or amends its listing. See 21 C.F.R. § 314.53(f). As the FDA has explained, there is no "statutory basis for a substantive agency review of patents," and the FDA "lack[s] expertise in patent matters" in any event. 68 Fed. Reg. 36,683 (2003); see also *Teva Pharm., USA, Inc.* v. *Leavitt*, 548 F.3d 103, 106 (D.C. Cir. 2008) (acknowledging FDA's "purely ministerial role" with respect to "the patent information supplied by NDA holders"). Consequently, in the absence of effective judicial review, brand-name manufacturers are free to submit overstated patent information to the FDA in order to block entry by generic competitors.

B. The Decision Below Threatens To Stifle Generic Competition By Enabling—And Thus Encouraging—Brand-Name Manufacturers To Block Generic Drugs That Do Not Infringe Any Of Their Patents

1. This case involves a particularly pernicious form of manipulative conduct that a brand-name manufacturer may engage in when it holds a patent that covers at least one but fewer than all of the methods for using a particular drug. As explained above, the Hatch-Waxman Act allows an ANDA applicant in this scenario to file a section viii statement indicating that the brand-name manufacturer's patent "does not claim a use for which the applicant is seeking approval." 21 U.S.C. § 355(j)(2)(A)(viii). Doing so permits the generic applicant to take advantage of an exception to the usual rule that the generic drug's label must be identical to that of its brand-name counterpart. See 21 U.S.C. § 355(j)(2)(A)(v) and (4)(G); see also U.S. Invitation Br. at 3-5, *PLIVA, Inc.* v. *Mensing*, No. 09-993 (cert. granted Dec. 10, 2010). A generic applicant that has filed a section viii statement may submit a proposed label to the FDA that omits reference to—*i.e.*, carves out—the patented methods of using the drug. See Pet. App. 5a. By omitting reference to the patented use, the generic manufacturer avoids infringement, which in turn allows it to avoid the filing of a paragraph IV certification that could delay approval of the ANDA.

To facilitate the processing of section viii statements, FDA regulations require brand-name manufacturers to include in the patent information sub-

mitted with an NDA a "description of the patented method of use." 21 C.F.R. § 314.53(c)(2)(ii)(P)(3). This description, known as a "use code narrative" or "use code," is then employed by the FDA in determining whether to approve a generic manufacturer's proposed carve-out label. Reflecting the broader principle that the FDA's role in listing patents is ministerial, the FDA defers entirely to the brand-name manufacturer's description of the scope of its patent. If there is any overlap between the proposed carve-out label and the use code submitted by the brand-name manufacturer, the FDA will not approve the section viii statement. Pet. App. 6a.

There is significant potential for mischief in this process, and this case illustrates that all too well. After the FDA had preliminarily accepted petitioners' section viii statement, respondents amended the use code associated with their unexpired patent to cover the uses for which petitioners sought approval. Although there is no question that respondents' use code is overbroad—and respondents in fact *concede that the uses for which petitioners sought approval would not infringe their patent*—respondents' erroneous use code led the FDA to reverse course and reject petitioners' section viii statement.

Congress has provided a method for generic manufacturers to deal with such gamesmanship. Section 355(j)(5)(C)(ii)(I) of Title 21 authorizes a generic manufacturer defending a patent-infringement suit to file a "counterclaim seeking an order requiring the [patent] holder to correct or delete the patent information submitted by the holder * * * on

the ground that the patent does not claim * * * an approved method of using the drug." By its terms, the statute authorizes a counterclaim seeking "correct[ion]" of patent information contained in the Orange Book whenever there is "an approved method of using the drug" that "the patent does not claim." The court of appeals nonetheless held that a generic manufacturer may assert a counterclaim only when the patent at issue does not claim *any* approved method of using the drug. See Pet. App. 12a.

That is wrong. As the dissent from the denial of rehearing en banc explained, the panel majority's conclusion effectively "eviscerates" section viii in many cases. Pet. App. 62a. So long as a brand-name manufacturer has a patent covering at least one approved method of using a drug, the manufacturer can "follow [respondents'] lead and draft exceedingly broad use codes" that will prevent any generic competitors from carving out unpatented uses for the drug. *Ibid.* Secure in the knowledge that overbroad descriptions will not be rejected (or even reviewed) by the FDA and cannot be challenged in court, brand-name manufacturers can be expected to submit ever broader patent descriptions.

Our prediction is not idiosyncratic. A recent report directed at investors in the brand-name drug industry greeted the decision below with enthusiasm and predicted that brand-name manufacturers will deliberately and successfully pursue this strategy to extend their lucrative monopolies on certain drugs. See Morgan Stanley Research Europe, *Pharmaceuticals: Potential Selective Upside for Industry post Prandin Ruling* 2 (Sept. 1, 2010) ("We anticipate that

several companies will extract significant [earnings per share] and [net present value] upside from utilization of PUC (Patent Use Code) narrative strategies."); see also *ibid.* ("[W]e anticipate increasing listing of 'use' patents in the Orange Book as the [brand-name] industry seeks to maximize any commercial gains.").[4]

This Court's immediate review is required to prevent brand-name manufacturers from exploiting the vacuum in oversight created by the decision below. As the petition explained (at 22), in recent years brand-name manufacturers have increasingly turned to filing method-of-use patents in an effort to extend their monopoly power as their patents on drug compounds expire. See Kurt R. Karst, *Analysis Shows Patent Use Codes Have Doubled Since August 2003* (July 8, 2010).[5] Thus, many brand-name manufacturers will be well placed and eager to employ the same manipulative tactics that respondents used here.

2. The panel majority floated two arguments in hopes of deflating the significance of its decision. Neither one withstands scrutiny.

First, there is no merit to the suggestion that paragraph IV litigation will provide an adequate substitute for a counterclaim seeking correction of

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[4] Available at http://www.fdalawblog.net/files/morgan-stanley-rpt---puc-decision.pdf.

[5] Available at http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2010/07/analysis-shows-patent-use-codes-have-doubled-since-august-2003--by-kurt-r-karst-httpwwwhpmcomvattorneycfmrid22.html.

overbroad patent information. See Pet. App. 14a, 16a. First of all, that suggestion overlooks the fact that infringement litigation (which is frequently spawned by a paragraph IV certification) carries with it an automatic 30-month stay of FDA approval of the generic manufacturer's ANDA. 21 U.S.C. § 355(j)(5)(B)(iii). The whole point of a section viii statement is that a generic manufacturer should be able to sell a drug *immediately* when it is marketed for an unpatented use. The prospect that the generic manufacturer may *ultimately* prevail, after long and costly infringement litigation, is cold comfort.

Moreover, the unavailability of a counterclaim to correct overbroad patent descriptions may well make it impossible for the generic manufacturer to prevail in many cases where, as here, the brand-name manufacturer has indisputably erred in describing what the patent actually covers. As explained above, if the FDA concludes that the section viii applicant's proposed labeling overlaps with a use code submitted by the brand-name manufacturer, the FDA will reject the section viii statement and the carve-out in the proposed labeling. The generic manufacturer will then be forced to market the drug with the same label used by the brand-name counterpart, which is by definition infringing with respect to the patented use. Thus, a generic manufacturer's only recourse is to abandon competition or try to demonstrate that the brand-name company's patent is invalid, even if the uses for which the generic manufacturer seeks FDA approval would in no way infringe the patent.

It is likewise impossible to explain away the significance of the court of appeals' decision by

asserting that the FDA somehow "gummed up the works." Pet. App. 20a (Clevenger, J., concurring); see also Pet. App. 14a (majority opinion) (suggesting that "Caraco's real complaint should lie with the FDA"). As the dissenting opinion explained, the FDA required respondents to modify their label for repaglinide to include a single, broad indication. See Pet. App. 47a. But the FDA never required respondents to amend the use code submitted with their NDA, which was the decisive factor in the FDA's decision not to approve petitioners' ANDA. See *id.* at 47a-48a.

Even if the FDA had introduced some complication, that would not diminish the adverse impact of the decision below. Nothing in the panel majority's opinion turned on the FDA's supposed role in respondents' amendment to the use code. Instead, the panel majority held broadly that 21 U.S.C. § 355(j)(5)(C)(ii)(I) never authorizes a counterclaim if the patent at issue claims at least one of the drug's approved uses—a conclusion that will apply no matter how badly the brand-name manufacturer misrepresents the scope of its patent, and no matter the reason it gives for having done so.

C. The Decision Below Effectively Invalidates A Crucial FDA Regulation And Undermines The FDA's Implementation Of The Hatch-Waxman Act

Certiorari is also warranted because the decision below threatens to disrupt the FDA's orderly implementation of the Hatch-Waxman Act. As noted above, an FDA regulation titled "Submission of

patent information" requires brand-name manufacturers to submit with an NDA a detailed list of "patent information." 21 C.F.R. § 314.53(c)(1)-(2). With respect to patents claiming a method of using the drug, the NDA applicant must submit not only the use code discussed above, but also an "[i]dentification of the specific section of the approved labeling for the drug product that corresponds to the method of use claimed by the patent submitted." 21 C.F.R. § 314.53(c)(2)(ii)(P)(2). The FDA has explained that this "claim-by-claim listing of method-of-use patents" is necessary to permit ANDA applicants "to assess whether they are seeking approval for a use claimed in the listed patent," and thus to "determine whether to submit a patent certification or a section viii statement." 68 Fed. Reg. 36,685 (2003). It is also necessary so that the FDA "can verify that the certification or statement is correct, and that only the appropriate methods of use are included in the proposed labeling for the ANDA." *Ibid.*

In the course of holding that petitioners could not assert a counterclaim under Section 355(j)(5)(C)(ii)(I), the panel majority reasoned that the statutory phrase "patent information" means only "the patent number and the expiration date" submitted by the NDA applicant. Pet. App. 15a (citing 21 U.S.C. § 355(b)(1)). The panel majority afforded no deference to the FDA's construction of the phrase "patent information" embodied in 21 C.F.R. § 314.53, even though that regulation was promulgated mere months before Congress passed the amendments that added Section

355(j)(5)(C)(ii)(I)'s counterclaim provision to the Hatch-Waxman Act. See Pet. App. 16a; Pet. App. 33a-38a (Dyk, J., dissenting). By construing the phrase patent information so narrowly, the panel majority's decision effectively invalidates the FDA's broader interpretation of that term in 21 C.F.R. § 314.53.

The practical implications of that erroneous conclusion will hamstring the FDA. As the FDA has explained, "[a] fundamental assumption of the Hatch-Waxman [Act] is that the courts are the appropriate mechanism for the resolution of disputes about the scope and validity of patents." 68 Fed. Reg. 36,683 (2003). But the panel majority's conclusion means that there will be no judicial forum available to resolve disputes over the scope of a brand-name manufacturer's use code narrative. By thus removing the only effective check on the submission of misleading patent descriptions for publication in the Orange Book, the decision below renders the FDA's patent listing process a conduit for misinformation. At the very least, the Court should not permit the decision below to stand without calling for the views of the FDA on the important issues implicated by this case.

D. The Decision Below Threatens To Impose Staggering Costs On American Consumers

The significance of the decision below extends beyond its immediate impact on the generic industry. It also threatens to deprive consumers of the important benefits of generic competition—namely, affordable prices for safe and effective generic drugs.

Prices of generic drugs are dramatically lower than the prices of their brand-name counterparts. According to FDA estimates, the entry of just two generic manufacturers into the market for a given drug "reduces the average generic price to nearly half the brand name price." FDA, *Generic Competition and Drug Prices* (Mar. 1, 2010).[6] "For products that attract a large number of generic manufacturers, the average generic price falls to 20% of the branded price and lower." *Ibid.*

The lower prices of generic drugs translate into massive aggregate benefits for American consumers. Today, roughly 75% of all U.S. prescriptions are filled with generic drugs, and domestic sales of generic drugs average more than $50 billion per year. See Jonathan D. Rockoff, *Prescription-Drug Sales Rise 5.1%*, Wall St. J., Apr. 2, 2010; Generic Pharmaceutical Ass'n, *Facts at a Glance*.[7] A recent study reported that generic drugs "saved the nation's health care system more than $824 billion dollars" over the last ten years, with savings of $139.6 billion in 2009 alone. IMS Health & Generic Pharmaceutical Ass'n, *Savings Achieved Through the Use of Generic Pharmaceuticals 2000-2009*, at 1 (July 2010).[8]

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[6] Available at http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm129385.htm.

[7] Available at http://www.gphaonline.org/about-gpha/about-generics/facts.

[8] Available at http://www.gphaonline.org/sites/default/files/GPhA%20Savings%20Study%20Book%20Updated%20Web%20FINAL%20Jul23%2010_0.pdf.

Of course, the flip side of the dramatic benefits associated with generic entry is that any *delay* in generic entry imposes enormous costs. Indeed, one commentator has estimated that, for a set of 21 widely prescribed prescription drugs, a one-year delay in the entry of generic competition "represents, under conservative assumptions, a transfer from consumers to producers of about $14 billion." C. Scott Hemphill, *An Aggregate Approach to Antitrust: Using New Data and Rulemaking to Preserve Drug Competition*, 109 Colum. L. Rev. 629, 650 (2009). By providing a roadmap for brand-name manufacturers seeking to block generic entry, the decision below threatens to impose these staggering costs on American consumers.

* * * *

Before the Hatch-Waxman Act's passage, generic drugs accounted for only about 12% of all prescriptions filled in the United States. See FDA, *Greater Access to Generic Drugs* (Jan. 2006).[9] Today, that figure is approximately 75%. The decision below, however, creates a serious roadblock to maintaining or furthering this success. This Court should grant review now to resolve this highly important question and to clear the way for generic manufacturers to continue to bring safe, effective, and affordable drugs to American consumers.

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[9] Available at http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143545.htm.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

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AMICUS CURIAE BRIEF

No. 10-844

IN THE

Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD., and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Petitioners,

v.

NOVO NORDISK A/S and NOVO NORDISK, INC.,
Respondents.

On Petition for a Writ of Certiorari
to the United States Court of Appeals
for the Federal Circuit

BRIEF OF *AMICUS CURIAE* MYLAN PHARMACEUTICALS INC. IN SUPPORT OF THE PETITION FOR CERTIORARI

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STATEMENT OF INTEREST*

Mylan is a manufacturer of generic drugs that frequently files Abbreviated New Drug Applications (ANDAs) under the Hatch-Waxman Act seeking approval of the Food and Drug Administration (FDA) to market drugs for particular uses. Mylan often relies on "section viii" statements when the methods of use that it proposes are not patented. *See* 21 U.S.C. § 355(j)(2)(A)(viii). The FDA, however, will not grant approval if a proposed use falls within the description of a patented method of use that is listed in the FDA's "Orange Book." The accuracy of Orange Book patent information is thus critical.

Regrettably, branded manufacturers often overstate the scope of their patents, and the FDA does not police the accuracy of Orange Book information. In *Mylan Pharmaceuticals, Inc. v. Thompson*, 268 F.3d 1323 (2002), the Federal Circuit held that generic drug manufacturers had no right to sue to correct Orange Book listings. The very next year, Congress responded by expressly authorizing ANDA applicants to file counterclaims to correct or delete erroneous Orange Book patent information. *See* 21 U.S.C. § 355(j)(5)(C)(ii)(I). The availability of such counterclaims serves as a much-needed check on branded drug manufacturers and deters them from supplying misinformation to the FDA.

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* No party or counsel for a party authored or contributed monetarily to the preparation or submission of any portion of this brief. Mylan gave all the parties' counsel of record notice of its intention to file this brief more than 10 days before it was due, and all parties have consented to the filing of this brief.

The decision below, however, has read the counterclaim provision extraordinarily narrowly, holding that correctable "patent information" is limited to patent numbers and expiration dates and that counterclaims are available only in extreme cases when no approved uses at all have been patented. The decision effectively eviscerates the counterclaim provision and enables incumbent branded manufacturers to block legitimate section viii applications with false Orange Book listings.

Mylan urges the Court to grant certiorari and reverse because the result, if upheld will be devastating to the generic drug industry and to consumers—and costly to taxpayers as well. The counterclaim provision may seem obscure at first blush, but it is critical to ensuring effective operation of the Hatch-Waxman Act.

SUMMARY OF ARGUMENT

Congress authorized ANDA applicants to counterclaim to "correct" Orange Book "patent information" that overstates patent coverage, not merely to "delete" listings where none of the approved uses is patented. Correctable "patent information" includes information about patents' scope, not merely their serial numbers and expiration dates. The term "patent information" should be read in light of Congress's purpose (to have patentees identify which drugs and methods remain patented so that ANDA applicants can avoid infringement), not in a vacuum. The courts should also defer to the FDA's longstanding construction of "patent information," which covers use code narratives and other patent-related information, not just serial numbers and expiration dates.

The Federal Circuit's artificially narrow construction will not only gut the counterclaim provision, but upset the careful balance of the Hatch-Waxman Act. If the decision in this case stands, brand-name drug manufacturers will be able to abuse the Orange Book listing system with impunity because the FDA does not review the accuracy of those listings. With no agency oversight and no judicial review, branded drug companies can and will deter and delay legitimate, noninfringing generic competition.

The practical ramifications are very significant. Section viii certifications are common and increasingly important. Patents on the chemical compositions of many leading drugs have expired, and branded drug companies have responded by seeking patents on uses of those drugs. The decision in this case effectively enables branded drug companies to delay generic competition for nonpatented uses, greatly increasing costs to consumers and taxpayers.

Review cannot await another case. Because the Federal Circuit has exclusive jurisdiction over these kinds of cases, there will be no next case. At a minimum, the Court should call for the views of the Solicitor General because this case raises important questions of competition and health care policy in which two agencies have already expressed interest.

ARGUMENT

A. Congress Did Not Limit Counterclaims to Extreme Cases in Which None of the Approved Uses Have Been Patented

Congress's 2003 amendments to the Hatch-Waxman Act authorized ANDA applicants to assert coun-

terclaims to "correct or delete the patent information submitted by the holder ... on the ground that the patent does not claim ... an approved method of using the drug." 21 U.S.C. § 355(j)(5)(C)(ii)(I)(bb). Naturally read, the statute authorizes relief when one or more of the approved uses is not claimed in a patent, despite its inclusion in the Orange Book. The Federal Circuit, however, has read it to apply only when *none* of the approved uses is patented. The latter reading may be linguistically *possible*, but it is strained and makes no sense when the language is read in context and in light of the underlying object and policy of the statute.

To begin with, the statutory text belies the Federal Circuit's conclusion that Congress intended to limit counterclaims to extreme cases in which a listed patent covers no approved uses whatsoever. In such cases, the remedy would be to delete the patent from the Orange Book entirely. But Congress authorized counterclaims to "correct" as well as to "delete" erroneous patent information. 21 U.S.C. § 355(j)(5)(C)(ii)(I). By authorizing correction as well as deletion, Congress plainly intended to cover situations where a listing is partly right and partly wrong.

Furthermore, the purpose of the counterclaim provision was to provide a remedy when patent holders submit erroneous information to the FDA about patent coverage of drugs or methods of using them. The goal was not simply to correct the Orange Book for the sake of correcting it, but to enable ANDA applicants to enter the market when the ANDA does not infringe. Under the Federal Circuit's narrow reading, a patentee may misidentify a patent as covering an approved use, yet competitors will have

no way to correct the misinformation or to file a section viii certification. That is the kind of abuse that Congress sought to eliminate and the kind of loophole that it intended to close. *See* 149 Cong. Rec. 31121, 31200 (Nov. 24, 2003) (sponsoring Sen. Schumer: "The provisions close loopholes in the law and end the abusive practices in the pharmaceutical industry which have kept lower-priced generics off the market and cost consumers billions of dollars.").

The majority below assumed that Congress merely intended to reverse the result on the particular facts of *Mylan v. Thompson*, but the statute was not limited to just those facts. *Mylan v. Thompson* was indeed a gross example of the problems with existing law, but it was far from the only abuse about which Congress was concerned. The year before, the Federal Trade Commission ("FTC") had issued a 129-page study describing a wide range of dubious strategies that branded drug manufacturers had used to delay generic entry.[1] Nothing in the legislative history of the 2003 amendment suggests that Congress limited its authorization of counterclaims to the particular facts of *Mylan v. Thompson*. The solution was general.[2]

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[1] *See* FTC, *Generic Drug Entry Prior to Patent Expiration* (July 2002), *available at* www.ftc.gov/os/2002/07/genericdrug study.pdf; *see also* 149 Cong. Rec. 15490, 15514 (Jun. 19, 2003) (Sen. McCain noting abuses).

[2] *See* Natalie M. Derzko, *The Impact of Recent Reforms of the Hatch-Waxman Regime on Orange Book Strategic Behavior and Pharmaceutical Innovation*, 45 IDEA 165 (2005) (describing the legislative history).

B. As the FDA Determined, "Patent Information" Includes Information About Patent Scope, Not Just Serial Numbers and Expiration Dates

Congress adopted the counterclaim provision to ensure that generic drug makers have judicial recourse to correct or delete misinformation about patent coverage that branded drug makers have submitted to the FDA. In holding that correctable "patent information" is limited to patent numbers and expiration dates and excludes the uses that the patents purportedly cover, the Federal Circuit has defied the language of the statute and the FDA's longstanding interpretation of "patent information."

The Hatch-Waxman Act requires NDA applicants to list patents claiming a drug or method of use "with respect to which a claim of patent infringement could reasonably be asserted." 21 U.S.C. § 355(b)(1)(G). The statute thus expressly contemplates that the patent holder will describe the scope of the patents and relate them to the drug or method of use for which approval is sought. The resulting Orange Book listings are supposed to notify later ANDA applicants which drugs or methods of use are patented so that those applicants can submit appropriate certifications under 21 U.S.C. § 355(j)(2)(A)(vii) and (viii). "Patent information" must be read in light of that purpose, not in a vacuum.

Furthermore, when Congress adopted the counterclaim provision in 2003, the FDA had already adopted a regulation (the Patent Listing Rule) that broadly construed the scope of "patent information" required under Hatch-Waxman. Under 21 C.F.R. § 314.53, the FDA required patentees to submit not

only patent numbers and expiration dates, but also use code narratives and other patent-related information. The FDA's interpretation deserves deference, as courts "have long recognized that considerable weight should be accorded to an executive department's construction of a statutory scheme it is entrusted to administer[.]" *Chevron U.S.A. Inc. v. Natural Res. Def. Council*, 467 U.S. 837, 844 (1984). What is more, Congress was not just constructively aware but actually aware of the FDA's broad reading of "patent information" when it adopted the amendment authorizing counterclaims to correct or delete erroneous "patent information."[3] Such awareness indicates that Congress intended to adopt the FDA's broad view of "patent information."

C. The Federal Circuit's Decision Will Have Pernicious Practical Effects

Certiorari should also be granted because the decision below will have terrible consequences. If left standing, it will allow brand-name drug manufacturers to abuse use codes with impunity, effectively blocking generic competition and providing unwarranted patent protection for drug uses that are not patented. The inevitable result will be restricted supply and higher prices for critical drugs.

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[3] *See Legislative and Regulatory Responses to the FTC Study on Barriers to Entry in the Pharmaceutical Marketplace: Hearing Before the S. Comm. on the Judiciary*, 108th Cong., 1st Sess. 19 (2003) (sponsoring Sen. Schumer: "The bill provides a critical complement to the work the FDA has done in clarifying its regulations on patent listing, but it goes much further.").

1. The Decision Below Will Deter and Delay Legitimate Competition

Congress recognized the signal importance of generic competition both when originally adopting the Hatch-Waxman Act in 1984 and when amending it in 2003 to authorize counterclaims to delete or correct misinformation in the Orange Book. As noted above, even before Congress adopted the counterclaim provision, the FTC had issued a study describing a broad range of anticompetitive strategies that branded manufacturers were using to delay generic entry, including the listing of patents that "do not appear to claim the approved drug product or an approved use of the drug."[4] The Federal Circuit's decision effectively ratifies this stratagem.

Under the decision below, a branded drug manufacturer may submit overly broad use descriptions covering both patented and unpatented methods of use, yet generic competitors cannot counterclaim to correct such misdescriptions. Counterclaims are an indispensable remedy because the FDA does not scrutinize Orange Book listings on grounds that it lacks expertise on patent issues. *See Purepac Pharm. Co. v. Thompson*, 354 F.3d 877, 885 (D.C. Cir. 2004) (FDA "refuses to determine independently what use a patent covers and instead accepts at face value the use claimed by the patent holder"); 21 C.F.R. § 314.53(f) (FDA "will not change the patent information in the list" unless the patentee requests).

With no FDA oversight and no judicial remedy, nothing will stop branded manufacturers from artifi-

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[4] *See* FTC generic drug study, *supra* note 1, at 40.

cially extending the scope of their patent protection. As one commentator recognized even before the decision in this case, "[i]nstead of appropriately assigning the use code, pioneers may be motivated to assign an extremely broad use code to its method of use, thereby optimizing patent protection."[5] After the Federal Circuit's decision, they will be especially motivated—and unimpeded.

For example, assume a branded manufacturer's patents on a compound and a method of using it to treat disease 1 have expired, but a patent on using it to treat disease 2 remains in force. If the statute worked as Congress intended, a generic drug maker could file a section viii certification and enter the market with a carve-out label limited to treating disease 1. The branded manufacturer, however, can stifle that competition by submitting an overbroad description covering both uses. The FDA will not approve the generic's ANDA because the proposed use falls within the Orange Book description submitted by the patent holder, even though the patent on its face does not cover the use of the drug to treat disease 1. The FDA also will not review the accuracy of the Orange Book description, and the Federal Circuit has now held that the courts are impotent too, even though Congress adopted the counterclaim provision to prevent just this type of chicanery.

Technically, the generic competitor may still file a paragraph IV certification of noninfringement, but

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[5] Julie Dohm, Comment, *Expanding the Scope of the Hatch-Waxman Act's Patent Carve-Out Exception to the Identical Drug Labeling Requirement: Closing the Patent Litigation Loophole*, 156 U. PA. L. REV. 151, 164 (2007).

that is cold comfort, as even the concurring judge below recognized, Pet. App. 19a–20a. Even though the generic manufacturer has no desire to promote the patented use of the drug, the statute normally will require it to match the original drug labeling covering both patented and unpatented uses. *See* 21 U.S.C. § 355(j)(2)(A)(v). The patentee will then claim that the generic has induced infringement by selling the drug with broad labeling that has no carve-out.

Mylan hopes that the courts would find remedies for such abuse, perhaps finding that the generic manufacturer lacked specific intent to induce infringement or, alternatively, that the patent is unenforceable for misuse. Those defenses, however, would be fraught with danger, and the law in those areas is unsettled.[6] Furthermore, paragraph IV litigation is expensive, time-consuming, and leads to an automatic 30-month stay of FDA approval under 21 U.S.C. § 355(j)(5)(B)(iii). That delay would not occur if the generic manufacturer could carve out the unpatented use under section viii. Ironically, but inevitably, generic entry will be stalled in the very cases where Congress sought to accelerate it.

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[6] Federal Circuit decisions broadly construing intent to induce infringement and narrowly construing patent misuse are now before this Court. *See Global-Tech Appliances, Inc. v. SEB, S.A.*, No. 10–6 (U.S.) (to be argued Feb. 23, 2011); *Princo Corp. v. ITC*, 616 F.3d 1318 (Fed. Cir. 2010) (en banc), *petition for cert. filed*, No. 10–898 (Jan. 5, 2011).

2. Blocking Generic Entry Will Have Broad and Harmful Effects on the Public at Large

Section viii certifications are common and becoming increasingly important. Many patents on the basic chemical composition of blockbuster drugs have expired or soon will. Foreseeing this, branded manufacturers have secured follow-on patents on particular methods of use in an effort to maintain "evergreen" patent protection.[7] Section viii certifications allow entrants to enter the market yet still respect incumbents' limited remaining patent rights. Moreover, section viii applications are especially useful and popular because, unlike paragraph IV certifications, they are not considered technical acts of infringement under 35 U.S.C. § 271(e)(2)(A) and thus do not automatically trigger the 30-month delay of FDA approval under 21 U.S.C. § 355(j)(5)(B)(iii).

As a practical matter, the decision below will severely reduce the availability of section viii applications, and the resulting lengthy delays in generic entry will result in significant, tangible costs to consumers and taxpayers. On average, generic drugs cost 80 to 85% less than brand-name drugs.[8] Thus, where, as here, generic entry is artificially delayed,

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[7] *See, e.g.*, Rebecca S. Yoshitani & Ellen S. Cooper, *Pharmaceutical Reformulation: The Growth of Life Cycle Management*, 7 HOUS. J. HEALTH L. & POL'Y 379 (2007) (describing patents procured by pharmaceutical companies to extend the length of patent protection on their products).

[8] *See* Somnath Pal, *Directions in Generic Drugs*, 35 U.S. PHARMACIST 8 (Jun. 17, 2010), *available at* http://www.uspharmacist.com/content/s/127/c/21064.

drug prices will remain artificially high. Branded drug companies claim they need patent protection as a reward for undertaking research, but that excuse rings hollow where patent protection on the use at issue has expired. In such cases, the patentee has already received its just reward. Strategic gamesmanship that improperly broadens and extends patent coverage should not be tolerated.

D. Certiorari Should Be Granted Now

The issues raised by the petition are critical to proper operation of the Hatch-Waxman Act. Congress overturned *Mylan v. Thompson* and authorized counterclaims because it recognized that its carefully balanced statutory scheme will not work if misinformation in the Orange Book cannot be corrected. The Federal Circuit's decision not only renders the counterclaim provision largely useless; it allows drug patent holders to nullify section viii and block entry even when a generic manufacturer seeks approval only for unpatented uses. Mylan urges the Court to grant certiorari and correct it now.

Waiting is not an option. Decisions in other areas may be refined as they percolate through later cases, and this Court sometimes refrains from granting review to see how the law develops. The decision here, however, rules out counterclaims in the vast majority of cases of Orange Book misuse. Moreover, the Federal Circuit has denied rehearing *en banc*, and no other court of appeals can hear these issues: an action to correct or delete Orange Book information must be brought as a counterclaim to a patent infringement claim, 21 U.S.C. § 355(j)(5)(C)(ii)(I)(bb), and the Federal Circuit has exclusive appellate juris-

diction over patent infringement claims, 28 U.S.C. § 1295(a)(1). If the decision below stands, counterclaims will not be allowed, and patently erroneous Orange Book listings will stand uncorrected. Certiorari should be granted now because there will be no next case tomorrow.

At a minimum, the Court should call for the views of the Solicitor General. This case raises important issues regarding both competition and health care policy. The FDA and the FTC have substantial interests, and the Federal Circuit's decision has already evoked serious concern from both agencies. The federal government can also speak to interest of federal taxpayers, who will pay much more for prescription drugs if the decision below is not reversed.

CONCLUSION

The petition for certiorari should be granted.

Respectfully submitted,

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January 27, 2011

AMICUS CURIAE BRIEF

JAN 2 1 2011
OFFICE OF THE CLERK

No. 10-844

IN THE
Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD. & SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Petitioners,

v.

NOVO NORDISK A/S & NOVO NORDISK, INC.,
Respondents.

On Petition for Writ of Certiorari to the U.S. Court of Appeals for the Federal Circuit

BRIEF OF TEVA PHARMACEUTICALS USA, INC. AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

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QUESTION PRESENTED

Does 21 U.S.C. § 355(j)(5)(D)(ii)(I) authorize an applicant for a proposed generic drug product to file a counterclaim against the manufacturer of a previously approved brand-name drug in which the generic applicant seeks to correct certain misleading patent information that the brand manufacturer submitted to the Food and Drug Administration ("FDA") pursuant to FDA's longstanding Hatch-Waxman Act regulations, or is the counterclaim provision unavailable for those purposes because FDA's longstanding regulations are invalid?

CORPORATE DISCLOSURE STATEMENT

Pursuant to this Court's Rules 24.1(b) and 29.6:

Petitioner Teva Pharmaceuticals USA, Inc. ("TUSA") is an indirect wholly owned subsidiary of Teva Pharmaceutical Industries Ltd. through the following parent companies: (i) Orvet UK Unlimited (Majority Shareholder), which in turn is directly owned by Teva Pharmaceuticals Europe B.V., which in turn is directly owned by Teva Pharmaceutical Industries Ltd.; and (ii) Teva Pharmaceutical Holdings Coöperatieve U.A. (Minority Shareholder), which in turn is directly owned by IVAX LLC, a direct subsidiary of TUSA. Teva Pharmaceutical Industries Ltd. is the only publicly traded direct or indirect parent company of TUSA, and no other publicly traded company owns more than 10% of its stock.

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STATEMENT OF INTEREST AND SUMMARY OF THE ARGUMENT[1]

Amicus curiae Teva Pharmaceuticals USA, Inc. ("Teva") is the world's largest manufacturer of generic drug products, and every year files dozens of abbreviated new drug applications ("ANDAs") seeking FDA approval to market generic versions of previously approved brand-name drugs in the United States. The content of Teva's ANDAs are governed by the Hatch-Waxman Act and FDA's Hatch-Waxman implementing regulations, which among other things require the company to make representations to FDA regarding the applicability of brand-name pharmaceutical patents to Teva's proposed generic drug products. One key goal of those requirements is to help ensure that expired patents, invalid patents, unenforceable patents, and otherwise inapplicable patents do not block FDA's ability to promptly approve generic drug products.

Needless to say, brand manufacturers generally lose significant revenue once a lower-priced generic equivalent becomes available. And over the years, certain brand companies thus sought to delay the onset of generic competition by manipulating their

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[1] All counsel of record received timely notice of the intent to file the brief, all parties have consented to its filing, and letters evincing such consent have been filed with the Clerk. Pursuant to this Court's Rule 37.6, *amicus* states that no counsel for a party authored any part of this brief and that neither such counsel, nor any party, nor any person or entity other than *amicus*, its members, or its counsel made a monetary contribution intended to fund the preparation or submission of this brief.

own patent submissions to FDA. *See, e.g.*, *aaiPharma Inc. v. Thompson*, 296 F.3d 227, 236 (4th Cir. 2002); *Andrx Pharms., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1377-78 (Fed. Cir. 2002); *Mylan Pharms., Inc. v. Thompson*, 268 F.3d 1323, 1327-29 (Fed. Cir. 2001).

The original Hatch-Waxman Act gave generic applicants no effective recourse. As the lower courts repeatedly held, generic applicants could not compel the "delisting" (or withdrawal) of improperly submitted brand-name patent information through either a counterclaim in patent litigation or by bringing a claim against FDA directly. *See aaiPharma*, 296 F.3d at 243; *Mylan*, 268 F.3d at 1332. Generic applicants thus found the approval of their products blocked by regulatory provisions that never should have applied to their applications, because those approval-timing provisions were triggered by patent filings that the brand manufacturers should not have made in the first place—but which the generic applicants were powerless to correct.

In 2003, Congress decided that enough was enough. As part of the Medicare Prescription Drug Improvement and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (the "MMA"), Congress for the first time gave generic applicants a shield against these tactics: a novel counterclaim right-of-action through which generic applicants can force brand companies to "correct or delete the patent information [they] submitted" to FDA. 21 U.S.C. § 355(j)(5)(D)(ii)(I) (the "counterclaim provision").

The Federal Circuit's deeply fractured decision in this case guts that critical provision. And *without*

even soliciting FDA's views, it effectively declares unlawful an FDA regulation that Congress knew about when it adopted the counterclaim provision and that otherwise plays what FDA itself has called an "essential" role in the Agency's administration of this complex regulatory scheme. The appellate court's decision ultimately frees brand companies to once again manipulate generic market entry—both by making improper patent submissions and, as a result of the court's effective invalidation of FDA's implementing regulations, by depriving generic applicants of the information they need to make appropriate patent certifications in the first place.

The impact of the appellate court's ruling has not been lost on industry observers. One Wall Street report predicts that the court's decision once again will allow "the innovative pharmaceutical industry to successfully delay US generic approval of select innovative drugs." *See* Morgan Stanley, *Pharmaceuticals: Potential Selective Upside For Industry Post Prandin Ruling* at 1 (Sept. 1, 2010). That outcome is impossible to square with the Hatch-Waxman Act's goal of expediting generic competition. And the financial consequences to the public will be enormous. As one recent study concluded, the widespread availability of generic drugs saved consumers $139.6 billion in 2009 alone—or nearly $382 million per day. *See* Generic Pharmaceutical Association, *Savings Achieved*

Through The Use Of Generic Pharmaceuticals, 2000-2009 at 1 (July 2010).[2]

If left uncorrected, the decision will directly impede Teva's ability to provide its affordable generic medications to the public. Congress gave generic applicants like Teva a specific mechanism to expedite FDA's approval for products that have multiple approved uses, by allowing them to sell their products for *unpatented* uses without being delayed by patents that cover *non-patented* uses that are not mentioned in the generic product's label. The appellate court's ruling eviscerates that "carve out" provision, in violation of both the language and the purpose of the applicable laws—and by allowing brand companies to mischaracterize the scope of their patents, will delay the approval of generic drugs despite the absence of any legitimate patent protection. Along with the millions of consumers who depend on the availability of safe and affordable generic drugs, Teva thus has a direct stake in the Court's resolution of this case, and respectfully urges this Court to grant the petition.

ABBREVIATED REGULATORY BACKGROUND

In an effort to balance the interest in promoting generic competition against the intellectual property rights of branded drug manufacturers, the Hatch-Waxman Act requires each generic applicant to submit a "certification" or "statement" regarding every patent that the product's brand manufacturer

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[2] *Available at* http://www.gphaonline.org/about-gpha/about-generica/case/generics-providing-savings-americans (last visited January 27, 2011).

has identified as claiming the approved brand-name drug. 21 U.S.C. § 355(j)(2)(A)(vii)-(viii). To make this system work, the statute requires brand manufacturers to submit patent information to FDA, 21 U.S.C. § 355(b)(1), and obligates FDA to "publish" the patent information it receives from brand companies. *Id.* § 355(j)(7)(A). FDA's official compendium of drug-related patent information is known as "the Orange Book," and generic applicants consult this official list in order to determine which patents require submissions. *Purepac Pharm. Co. v. Thompson*, 354 F.3d 877, 880 (D.C. Cir. 2004).

At the time it established the patent-certification regime, Congress recognized that not all pharmaceutical patents are created equal. On one hand, some drug patents claim the approved drug product's active pharmaceutical ingredient (the "drug substance"), and thus would be infringed *every time* another person manufactures or markets an identical drug substance (assuming the patent's underlying validity and enforceability). On the other hand, some drug patents merely claim a method of using the approved drug product, and thus *would not* be infringed if the identical drug substance were manufactured or marketed for unclaimed uses.

In order to promote the speedy approval of generic products for such unclaimed uses, the Hatch-Waxman Act and FDA regulations sharply distinguish between drug-substance patents and method-of-use patents. Generic applicants who wish to enter the market before an Orange Book-listed drug-substance patent expires must submit a so-called "Paragraph IV certification" challenging the patent's validity or enforceability, or asserting that

their proposed generic drug would not infringe the patent. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV); 21 C.F.R. § 314.94(a)(12)(i).

Such certifications, however, carry significant risks. The first Paragraph IV challenger bears substantial research-and-development and legal costs to design around and/or contest the validity or enforceability of a drug-substance patent. And if those efforts succeed, merely filing such a certification is an act of infringement that could result in years of costly patent litigation. *See* 35 U.S.C. § 271(e); *see also Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 678 (1990). Indeed, the statute encourages brand manufacturers to file patent-infringement lawsuits: Where the brand manufacturer promptly sues a Paragraph IV challenger, FDA may not approve the ANDA for either 30 months or until the patent is declared invalid, not infringed, or unenforceable, whichever comes first. 21 U.S.C. § 355(j)(5)(B)(iii). This period of delay is known as the "thirty-month stay," and in many cases, its application postpones generic entry even after FDA has completed its scientific review of the generic drug and determined that—but for the pending patent litigation—the generic product could be approved for sale.

In contrast to their treatment of drug-substance patents, both the statute itself and FDA's implementing regulations give applicants a choice when addressing method-of-use patents. They can file either a Paragraph IV certification to such a patent (and thereby obtain approval for all previously approved methods of use), *see* 21 U.S.C. § 355(j)(2)(A)(vii)(IV), or a so-called "Section viii

statement" that carves out the patent-protected use from the generic product's labeling and thereby authorizes immediate FDA approval for any approved method of use not covered by the patent. *Id.* § 355(j)(2)(A)(viii); 21 C.F.R. § 314.94(a)(12)(iii); *see also Purepac*, 354 F.3d at 880 (explaining that Section viii statements are "attractive" because they facilitate prompt generic market entry). Section viii statements are particularly appealing because they avoid any possibility of a thirty-month stay: By definition, a generic company that "carves out" a patented use from its label is not challenging any patent covering that use, and there is thus no possibility of a patent suit that would trigger the thirty-month stay.

The complex interplay between Paragraph IV and Section viii filings has plagued FDA throughout Hatch-Waxman's nearly 30-year history. Given the statutory dichotomy between drug-substance and method-of-use patents, it is essential for FDA to distinguish between those types of patents at the threshold. After all, if the Agency does not know whether a given drug patent covers the drug-substance or merely claims a method-of-use—and, for method-of-use patents, *which* particular method of use the patent claims—it would be virtually impossible for FDA to determine whether a Section viii statement is permissible in the first instance, and if so, which use or uses can be carved out through a Section viii statement.

As both FDA and the Federal Circuit have recognized, however, problems commonly arise in this area because FDA has no patent-law expertise and therefore lacks the institutional capacity to

determine the scope of pharmaceutical patents. *See, e.g.*, *Apotex, Inc. v. Thompson*, 347 F.3d 1335, 1347-50 (Fed. Cir. 2003); *see also* Food and Drug Administration, *Applications for FDA Approval to Market a New Drug—Final Rule* ("*Final Rules*"), 68 Fed. Reg. 36676, 36683 (June 18, 2003). Accordingly, FDA long ago adopted a "ministerial role" regarding patent information.

Under this approach, FDA relies exclusively on the brand manufacturer's representations about the scope of a given patent. *Apotex*, 347 F.3d at 1347. But in order to effectively administer the dichotomy between Paragraph IV and Section viii, FDA requires brand manufacturers to submit information to FDA about the type of patent it asserts as claiming the branded drug (*i.e.*, drug substance or method of use) and, for method-of-use patents, the particular method of use claimed. 21 C.F.R. § 314.53 ("Submission of Patent Information"); *see also Final Rules*, 68 Fed. Reg. at 36681-83; Food and Drug Administration, *Applications for FDA Approval to Market a New Drug—Proposed Rule* ("*Proposed Rules*"), 67 Fed. Reg. 65448, 65448-54 (Oct. 24, 2002).

As set forth below, the Federal Circuit's decision effectively invalidates these crucial regulations.

ARGUMENT

The Federal Circuit Misconstrued The Statute's Counterclaim Provision And Improperly Invalidated FDA's Longstanding Implementing Regulations Without Even Soliciting The Agency's Views.

All four of the Federal Circuit's opinions in this case recognize that FDA's ministerial approach to

patent listings enables brand manufacturers to postpone generic market entry by submitting improper patent information to FDA. And all four of its opinions likewise recognize that Congress intended the MMA's counterclaim provision, 21 U.S.C. § 355(D)(ii)(I), to thwart such manipulation by allowing generic applicants to seek a court order requiring the brand manufacturer to correct or delete improperly submitted patent information. *See* Pet. App. 13a (majority opinion); Pet. App. 21a (Clevenger, J., concurring); Pet. App. 22a (Dyk, J., dissenting); Pet. App. 57a-58a (Gajarsa, J., dissenting from denial of rehearing *en banc*). The majority and the dissenters disagreed about the scope of the cure Congress gave generic manufacturers when it enacted the MMA, and the dissenters clearly got it right.

As Judges Dyk and Gajarsa recognized, the majority's narrow interpretation of the phrase "patent information submitted by the [brand manufacturer]" once again enables the very kind of manipulation Congress sought to thwart. Pet. App. 22a (Dyk, J., dissenting) ("[T]he majority ... now construes the statute contrary to its manifest purpose and allows the same manipulative practices to continue in the context of method patents."); Pet. App. 58a-59a (Gajarsa, J., dissenting from denial of rehearing *en banc*) ("The majority's opinion construes the counterclaim provision contrary to its manifest Congressional purpose. That construction renders 21 U.S.C. § 355(j)(2)(A)(viii) ("Section viii") carve-out statements a virtual nullity and leaves generic drug manufacturers without a remedy to challenge inaccurate Orange Book listings with respect to method of use patents.").

More important, the majority's interpretation of the statute conflicts with settled canons of interpretation, the statute's legislative history, and FDA's implementing regulations. Pet. App. 33a-39a (Dyk, J., dissenting); Pet. App. 63a-64a (Gajarsa, J., dissenting from denial of rehearing *en banc*). Indeed, by declaring FDA's patent-submission regulation inconsistent with the statute, the appellate court's opinion unquestionably will undermine FDA's ability to administer this regulatory regime.

A. The Federal Circuit Impermissibly Disregarded FDA's Interpretation Of The Hatch-Waxman Act's Patent-Submission Provisions.

As Judge Dyk explained in dissent, and as this Court long ago made clear, Congress is presumed to incorporate—rather than abrogate—prior agency interpretations. Pet. App. 37a & nn.11-12 (Dyk, J., dissenting) (citing *Traynor v. Turnage*, 485 U.S. 535, 546 (1988); *United States v. Bd. of Comm'rs of Sheffield, Ala.*, 435 U.S. 110, 131-35 (1978); *Cammarano v. United States*, 358 U.S. 498, 510 (1959); *Hartley v. Comm'r*, 295 U.S. 216, 220 (1935)). The appellate court, however, inexplicably disregarded that presumption here.

As set forth above, FDA's pre-MMA Hatch-Waxman regulations implemented the statute's patent-submission requirements at 21 U.S.C. § 355(b)-(c) by requiring brand manufacturers to submit patent information beyond the patent's number and expiration date—including information regarding any approved methods of use covered by method-of-use patents. 21 C.F.R. § 314.53. The relevant provisions of that regulation were:

consistent with FDA's prior practice between 1994 and 2003; proposed more than a year before the MMA became effective, *see Proposed Rules*, 67 Fed. Reg. at 65448, 65457 (explaining the proposed regulation and noting that "[o]ur principal legal authority for the proposed rule exists at sections 505 and 701 (21 U.S.C. 371) of the act. Section 505(b) of the act describes the contents of an NDA and 505(b)(2) applications, including the patent listing and patent certification requirements"); and finalized six months before the MMA became effective. *See Final Rules*, 68 Fed. Reg. at 36676, 36697-98 ("Our principal legal authority for the final rule is section 505 of the act, in conjunction with our general rulemaking authority in section 701(a) (21 U.S.C. 371) of the act. Section 505(b) and (c) of the act describes the contents of an NDA and 505(b)(2) application, including the patent submission and patent certification requirements.").

The appellate court offered no basis for thinking that Congress intended *sub silentio* to abrogate FDA's prior interpretation of the law when it passed the MMA. Instead, the panel majority sought to downplay Congress's awareness of FDA's prior interpretation of the statute's patent-submission requirements by deeming it to be no more than an "'opaque timing observation.'" Pet. App. 16a (quoting *Wyeth v. Kappos*, 591 F.3d 1364, 1372 (Fed. Cir. 2010)).

That was error. FDA's prior interpretation is not significant merely because it preceded the MMA. To the contrary, it matters because it bears directly on the meaning of the counterclaim provision's reference to the "patent information submitted by

[brand manufacturers]," 21 U.S.C. § 355(j)(5)(D)(II)(i), since Congress chose that language with full awareness that the "patent information submitted by [brand manufacturers]" included method-of-use information under FDA's regulations. Again, it is well-settled that Congress presumably incorporates prior agency interpretations, and the majority's attempt to dismiss that presumption as an "opaque timing observation"—when the presumption *necessarily* relates to timing—cannot be reconciled with this Court's longstanding case law.

Indeed, that presumption is virtually conclusive here, because the statute's legislative history demonstrates that the MMA's sponsors explicitly embraced FDA's regulations. Pet. App. 36a (Dyk, J., dissenting) ("Congress was well aware of [FDA's] regulatory interpretation of 'patent information' when it enacted the counterclaim provision.") (collecting sources). Congress drew heavily on FDA's expertise in crafting the MMA amendments, including the provisions at issue here. During the congressional hearings and debates over the MMA, senior FDA officials carefully detailed the Agency's current practices concerning the submission of patent information to the Agency. As the FDA's Chief Counsel thus explained, FDA's final regulation on patent submissions set forth "the patent information required to be submitted and ... does not require claim-by-claim listing on the declaration form *except for method-of-use patents claiming approved methods of use.*" S. Hrg. 108-390, Examining the Senate And House Versions of the "Great Access to Affordable Pharmaceuticals Act": Hearing Before the Committee on the Judiciary

United States Senate, 108th Cong., at 137-38 (Aug. 1, 2003) (statement of FDA Chief Counsel Daniel Troy).[3]

Moreover, he explained, nothing in the MMA would impact FDA's prior implementation of the statute's patent-submission requirements:

> The legislation, included as part of the Medicare bills in the House and Senate, does not address all of the provisions in the final rule. If such legislation were to pass, based on our review, we believe that *only the 30-month stay provision of the final rule would be impacted.*

Id. at 10 (emphasis added).

Congress in turn expressly sanctioned FDA's implementing regulations, by indicating that the law was intended to augment—rather than abrogate—them: "The bill provides *a critical complement* to the work the FDA has done in clarifying its regulations on patent listing." S. Hrg. 108-250, Legislative and Regulatory Responses to the FTC Study on Barriers to Entry in the Pharmaceutical Marketplace: Hearing Before the S. Comm. on the Judiciary, 108th Cong., at 19 (June 17, 2003) (statement of Sen. Schumer) (emphasis added).[4]

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[3] Reprint *available at* http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_senate_hearings&docid=f:91832.pdf (last visited January 26, 2011).

[4] Reprint *available at* http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_senate_hearings&docid=f:91212.pdf (last visited January 26, 2011).

As Judge Gajarsa thus recognized, the Federal Circuit's interpretation of the statutory scheme is unsustainable "given Congress's explicit approval of those regulations." Pet. App. 63a (Gajarsa, J., dissenting from denial of rehearing *en banc*).

B. The Federal Circuit's Effective Invalidation Of FDA's Patent-Submission Regulation Jeopardizes FDA's Ability To Administer This Complex Statutory Scheme.

Perhaps because it recognized those deficiencies in its analysis, the panel majority went further: It effectively declared that FDA's patent-submission regulation is unlawful, by baldly asserting that "this court owes no deference ... to agency interpretations at odds with the plain language of the statute itself." Pet. App. 16a (quotation omitted).

It would be hard to overstate the radical implications of that holding. Without even bothering to solicit (much less consider) the government's views—and without any apparent consideration of the Agency's 2,200-word regulatory justification for its patent-submission rules, *see Final Rules*, 68 Fed. Reg. at 36,681-83—a fractured panel of the Federal Circuit struck down a now-firmly established FDA regulation and held that the Agency cannot lawfully compel brand manufacturers to submit method-of-use information at all. *See id.*

The appellate court's ill-advised decision already is complicating FDA's ability to administer the statutory scheme. Pet. 26-27 (discussing recent statements by FDA's principal Hatch-Waxman counsel concerning the impact of this case on the Agency). And that is no surprise—FDA adopted its

implementing regulations precisely to avoid the problems it now is experiencing.

> To effectively implement the certification and section viii statement provisions set out in the statute, *we must have* adequate information concerning method-of-use patents.... Since the *Purepac* case and other instances have raised questions about what aspects of the approved drug are claimed by a listed use patent, we believe that *it is necessary* that an NDA holder submit more specific information on the approved methods of use protected by a submitted patent. *Only with this information can we determine what submission is required of the ANDA and 505(b)(2) applicants referencing the approved drug.*

Final Rules, 68 Fed. Reg. at 36682-83 (emphasis added); *see also id.* at 36682 (discussing *Purepac Pharm. Co. v. Thompson*, 238 F. Supp. 2d 191 (D.D.C. 2002)).

Indeed, as FDA long ago explained, knowing in advance what patent certifications generic applicants may submit is critical, because the different types of submissions lead to significant differences in the timing of approval—and because any uncertainty inevitably delays generic market entry. *Id.* at 36682; *id.* at 36685 ("The specific method-of-use claims are essential to our review because sections 505(j)(2)(A)(viii) and 505(b)(2)(B) of the act allow ANDA and 505(b)(2) applicants to file statements which assert that the method-of-use patent does not

claim a use for which the applicant is seeking approval.").

Unless this Court grants the petition, however, the panel majority's bald rejection of FDA's patent-submission regulation will remain the law—sowing confusion for both FDA and the generic industry over what certifications are required; generating unnecessary and inefficient litigation over threshold filing requirements; and ultimately delaying the public's access to affordable generic drugs.

CONCLUSION

For the foregoing reasons, this Court should grant the writ and reverse the Federal Circuit's decision.

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JOINT APPENDIX

Supreme Court, U.S.
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No. 10-844

In the Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD., ET AL.,
PETITIONERS

v.

NOVO NORDISK A/S, *ET AL.*, RESPONDENTS

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

JOINT APPENDIX
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UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S ET AL.
Plaintiff,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD.,
Defendant.

Date Filed 06/09/2005
Civil Docket for Case #: 2:05 CV 40188-AC-DAS

RELEVANT DOCKET ENTRIES

DATE	#	DOCKET TEXT
06/09/2005	1	COMPLAINT filed by Novo Nordisk A/S, Novo Nordisk, Incorporated against Caraco Pharmaceutical Laboratories, Limited, Receipt No. 526960. (THal,) (Entered: 06/13/2005)
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07/21/2005	7	ANSWER to Complaint with Affirmative Defenses, COUNTERCLAIM filed by Caraco Pharmaceutical Laboratories, Limited against all plaintiffs by Caraco Pharmaceutical Laboratories, Limited. (Witus, Morley) (Entered: 07/21/2005)

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08/18/2005	13	AMENDED ANSWER to Complaint 1 Complaint with Affirmative Defenses, COUNTERCLAIM filed by Caraco Pharmaceutical Laboratories, Limited, Caraco Pharmaceutical Laboratories, Limited against Novo Nordisk A/S, Novo Nordisk, Incorporated by Caraco Pharmaceutical Laboratories, Limited, Caraco Pharmaceutical Laboratories, Limited. (Witus, Morley) (Entered: 08/18/2005)
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DATE	#	DOCKET TEXT
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06/29/2009	337	MOTION to Dismiss Caraco's Fourth Counterclaim, MOTION to Strike Caraco's Sixth Affirmative Defense by Novo Nordisk A/S, Novo Nordisk, Incorporated. (Attachments: # 1 Proposed Order) (Krevitt, Josh) (Entered: 06/29/2009)
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DATE	#	DOCKET TEXT
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09/24/2009	422	NOTICE of Correction re 420 Memorandum and Order denying Motion for Partial Summary Judgment. (JOwe) (Entered: 09/24/2009)

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09/25/2009	423	ORDER and Injunction. Signed by District Judge Avern Cohn. (JOwe) (Entered: 09/25/2009)
09/29/2009	424	NOTICE OF APPEAL by Novo Nordisk A/S, Novo Nordisk, Incorporated. Receipt No: 0645000000002172307 - Fee: $ 455 - Fee Status: Fee Paid. (Attachments: # 1 Exhibit A) (Krevitt, Josh) (Entered: 09/29/2009)
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06/08/2010		Minute Entry - Bench Trial held on 6/8/2010, Set Deadlines/Hearings: (Bench Trial continuation set for 6/9/2010 09:00 AM before District Judge Avern Cohn) before District Judge Avern Cohn. (Court Reporter Sheri Ward) (JOwe) (Entered: 06/09/2010)
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06/09/2010		Minute Entry - Bench Trial held on 6/9/2010, Set Deadlines/Hearings: (Bench Trial continuation set for 6/10/2010 09:00 AM before District Judge Avern Cohn) before District Judge Avern Cohn. (JOwe) (Entered: 06/09/2010)
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08/11/2010		Minute Entry - Bench Trial completed on 8/11/2010 before District Judge Avern Cohn. (Court Reporter Sheri Ward) (JOwe) (Entered: 08/11/2010)
		* * * *
09/16/2010	503	MEMORANDUM and ORDER Signed by District Judge Avern Cohn. (SJa) (Entered: 09/16/2010)
09/30/2010	504	STIPULATION AND ORDER. Signed by District Judge Avern Cohn. (SJa) (Entered: 09/30/2010)
09/30/2010	505	STATEMENT of Undisputed Facts Concerning Subject Matter Jurisdiction by Caraco Pharmaceutical Laboratories, Limited, Sun Pharmaceutical Industries, Limited (Attachments: # 1 Index of Exhibits Index of Exhibits, # 2 Exhibit 1 - Feb 9, 2005 ANDA PIV Certification , # 3 Exhibit 2 - FDA Letter Dated Apr. 7, 2005, # 4 Exhibit 3 – Apr. 26, 2005 Notice Ltr, # 5

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		* * * *
10/06/2010	507	MEMORANDUM and ORDER Denying Plaintiffs' 478 MOTION to Dismiss for Lack of Subject Matter Jurisdiction Signed by District Judge Avern Cohn. (MWil) (Entered: 10/06/2010)
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DATE	#	DOCKET TEXT
01/19/2011	523	DECISION Signed by District Judge Avern Cohn. (JOwe) (Entered: 01/19/2011)
01/19/2011	524	JUDGMENT Signed by District Judge Avern Cohn. (JOwe) (Entered: 01/19/2011)
01/26/2011	525	NOTICE OF APPEAL by Novo Nordisk A/S, Novo Nordisk, Incorporated re 524 Judgment. Receipt No: 0645-2814100 - Fee: $ 455 - Fee Status: Fee Paid. (Attachments: # 1 Exhibit A - Judgment) (Sitzman, Michael) (Entered: 01/26/2011)

* * * *

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

NOVO NORDISK,
Plaintiff-Appellant,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendant-Appellee.

Court of Appeals
Docket No. 2010-1001
Docketed: 10/05/2009

RELEVANT DOCKET ENTRIES

DATE	#	DOCKET TEXT
		* * * *
10/09/2009	19	Ordered that: The injunction is temporarily stayed pending this court's review of stay of injunction. The motion to stay trial court proceedings is denied. Service: by Court on 10/9/2009
		* * * *

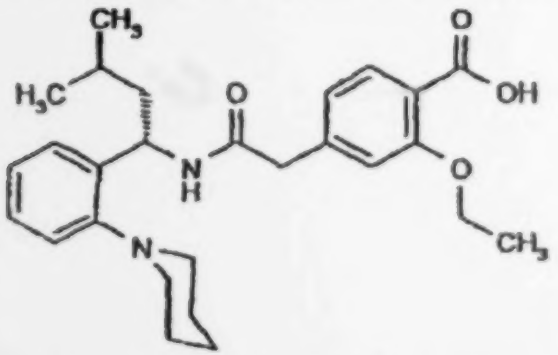
DATE		DOCKET TEXT
07/29/2009	78	Precedential Order: Appellees' combined petition for panel rehearing and rehearing en banc is denied. By: court en banc. Per Curiam. Gajarsa, Circuit Judge, with whom Dyk, Circuit Judge, joins, dissents. Service: by Court on 7/29/2010.
		* * * *
04/14/2010		Disposition: Reversed and Vacated; by Panel
		* * * *
		Rehearings
05/14/2010	46	Appellees [Caraco Pharmaceutical Laboratories, Ltd. and Sun Pharmaceutical Industries, Ltd.]-Combined Petition for Rehearing and Rehearing En Banc. Mail Service-5/14/2010. Filed: 5/14/2010.
		Response requested from: Appellants (Novo Nordisk A/S and Novo Nordisk Inc.) Response due: 6/1/2010. Response filed: 6/1/2010
	77	Petition/En Banc Action: Denied/Denied on 7/29/2010.

PRANDIN®
(repaglinide) Tablets (0.5, 1, and 2 mg)
Rx only

DESCRIPTION

PRANDIN® (repaglinide) is an oral blood glucose-lowering drug of the meglitinide class used in the management of type 2 diabetes mellitus (also known as non-insulin dependent diabetes mellitus or NIDDM). Repaglinide, S(+)2-ethoxy-4(2((3-methyl-1-(2-(1-piperidinyl) phenyl)- butyl) amino)-2-oxoethyl) benzoic acid, is chemically unrelated to the oral sulfonylurea insulin secretagogues.

The structural formula is as shown below:



Repaglinide is a white to off-white powder with molecular formula C_{27} H_{36} N_2 O_4 and a molecular weight of 452.6. PRANDIN tablets contain 0.5 mg, 1 mg, or 2 mg of repaglinide. In addition each tablet contains the following inactive ingredients: calcium hydrogen phosphate (anhydrous), microcrystalline cellulose, maize starch, polacrilin potassium, povidone, glycerol (85%), magnesium stearate, meglumine, and poloxamer. The 1 mg and 2 mg tablets contain iron oxides (yellow and red, respectively) as coloring agents.

CLINICAL PHARMACOLOGY

Mechanism of Action

Repaglinide lowers blood glucose levels by stimulating the release of insulin from the pancreas. This action is dependent upon functioning beta (ß) cells in the pancreatic islets. Insulin release is glucose-dependent and diminishes at low glucose concentrations.

Repaglinide closes ATP-dependent potassium channels in the ß-cell membrane by binding at characterizable sites. This potassium channel blockade depolarizes the ß-cell, which leads to an opening of calcium channels. The resulting increased calcium influx induces insulin secretion. The ion channel mechanism is highly tissue selective with low affinity for heart and skeletal muscle.

Pharmacokinetics

Absorption: After oral administration, repaglinide is rapidly and completely absorbed from the gastrointestinal tract. After single and multiple oral doses in healthy subjects or in patients, peak plasma drug levels (C_{max}) occur within 1 hour (T_{max}). Repaglinide is rapidly eliminated from the blood stream with a half-life of approximately 1 hour. The mean absolute bioavailability is 56%. When repaglinide was given with food, the mean T_{max} was not changed, but the mean C_{max} and AUC (area under the time/plasma concentration curve) were decreased 20% and 12.4%, respectively.

Distribution: After intravenous (IV) dosing in healthy subjects, the volume of distribution at steady state (V_{ss}) was 31 L, and the total body clearance (CL)

was 38 L/h. Protein binding and binding to human serum albumin was greater than 98%.

Metabolism: Repaglinide is completely metabolized by oxidative biotransformation and direct conjugation with glucuronic acid after either an IV or oral dose. The major metabolites are an oxidized dicarboxylic acid (M2), the aromatic amine (M1), and the acyl glucuronide (M7). The cytochrome P-450 enzyme system, specifically 2C8 and 3A4, have been shown to be involved in the N-dealkylation of repaglinide to M2 and the further oxidation to M1. Metabolites do not contribute to the glucose-lowering effect of repaglinide.

Repaglinide appears to be a substrate for active hepatic uptake transporter (organic anion transporting protein OATP1B1).

Excretion: Within 96 hours after dosing with ^{14}C-repaglinide as a single, oral dose, approximately 90% of the radiolabel was recovered in the feces and approximately 8% in the urine. Only 0.1% of the dose is cleared in the urine as parent compound. The major metabolite (M2) accounted for 60% of the administered dose. Less than 2% of parent drug was recovered in feces.

Pharmacokinetic Parameters: The pharmacokinetic parameters of repaglinide obtained from a single-dose, crossover study in healthy subjects and from a multiple-dose, parallel, dose-proportionality (0.5, 1, 2 and 4 mg) study in patients with type 2 diabetes are summarized in the following table:

Parameter	Patients with type 2 diabetes[a]
Dose 0.5 mg 1 mg 2 mg 4 mg	$AUC_{0\text{-}24\ hr}$ Mean ±SD (ng/mL*hr): 68.9 ± 154.4 125.8 ± 129.8 152.4 ± 89.6 447.4 ± 211.3
Dose 0.5 mg 1 mg 2 mg 4 mg	$C_{max0\text{-}5\ hr}$ Mean ±SD (ng/mL): 9.8 ± 10.2 18.3 ± 9.1 26.0 ± 13.0 65.8 ± 30.1
Dose 0.5 - 4 mg	$T_{max0\text{-}5\ hr}$ Means (SD) 1.0 - 1.4 (03 - 0.5) hr
Dose 0.5 - 4 mg	$T_{1/2}$ Means (Ind Range) 1.0- 1.4 (0.4 - 8.0) hr
Parameter	**Healthy Subjects**
CL based on i.v.	38 ± 16 L/hr
V_{ss} based on i.v.	31 ± 12 L
AbsBio	56 ± 9%

a: dosed preprandially with three meals

CL = total body clearance
V_{ss} = volume of distribution at steady state
AbsBio = absolute bioavailability

These data indicate that repaglinide did not accumulate in serum. Clearance of oral repaglinide did not change over the 0.5 - 4 mg dose range, indicating a linear relationship between dose and plasma drug levels.

Variability of Exposure: Repaglinide AUC after multiple doses of 0.25 to 4 mg with each meal varies over a wide range. The intra-individual and inter-individual coefficients of variation were 36% and 69%, respectively. AUC over the therapeutic dose range included 69 to 1005 ng/mL*hr, but AUC exposure up to 5417 ng/mL*hr was reached in dose escalation studies without apparent adverse consequences.

Special Populations:

Geriatric: Healthy volunteers were treated with a regimen of 2 mg taken before each of 3 meals. There were no significant differences in repaglinide pharmacokinetics between the group of patients <65 years of age and a comparably sized group of patients ≥65 years of age. (See **PRECAUTIONS, Geriatric Use**)

Pediatric: No studies have been performed in pediatric patients.

Gender: A comparison of pharmacokinetics in males and females showed the AUC over the 0.5 mg to 4 mg dose range to be 15% to 70% higher in females with type 2 diabetes. This difference was not reflected in the frequency of hypoglycemic episodes (male: 16%; female: 17%) or other adverse events. With respect to gender, no change in general dosage recommendation is indicated since dosage for each patient should be individualized to achieve optimal clinical response.

Race: No pharmacokinetic studies to assess the effects of race have been performed, but in a U.S. 1-year study in patients with type 2 diabetes, the blood glucose-lowering effect was comparable between Caucasians (n=297) and African-Americans (n=33). In a U.S. dose-response study, there was no apparent dif-

ference in exposure (AUC) between Caucasians (n=74) and Hispanics (n=33).

Drug-Drug Interactions:

Drug interaction studies performed in healthy volunteers show that PRANDIN had no clinically relevant effect on the pharmacokinetic properties of digoxin, theophylline, or warfarin. Co-administration of cimetidine with PRANDIN did not significantly alter the absorption and disposition of repaglinide.

Additionally, the following drugs were studied in healthy volunteers with co-administration of PRANDIN. Listed below are the results:

CYP2C8 and CYP3A4 Inhibitors/Inducer

Gemfibrozil and Itraconazole: Co-administration of gemfibrozil (600 mg) and a single dose of 0.25 mg PRANDIN (after 3 days of twice-daily 600 mg gemfibrozil) resulted in an 8.1-fold higher repaglinide AUC and prolonged repaglinide half-life from 1.3 to 3.7 hr. Co-administration with itraconazole and a single dose of 0.25 mg PRANDIN (on the third day of a regimen of 200 mg initial dose, twice-daily 100 mg itraconazole) resulted in a 1.4-fold higher repaglinide AUC. Co-administration of both gemfibrozil and itraconazole with PRANDIN resulted in a 19-fold higher repaglinide AUC and prolonged repaglinide half-life to 6.1 hr. Plasma repaglinide concentration at 7 h increased 28.6-fold with gemfibrozil co-administration and 70.4-fold with the gemfibrozil-itraconazole combination (see **CONTRAIN-DICATIONS, PRECAUTIONS, Drug-Drug Interactions**).

Fenofibrate: Co-administration of 200 mg fenofibrate with a single dose of 0.25 mg repaglinide (after

5 days of once daily fenofibrate 200 mg) resulted in unchanged AUC and C_{max} values for both drugs.

Ketoconazole: Co-administration of 200 mg ketoconazole and a single dose of 2 mg PRANDIN (after 4 days of once daily ketoconazole 200 mg) resulted in a 15% and 16% increase in repaglinide AUC and C_{max}, respectively. The increases were from 20.2 ng/mL to 23.5 ng/mL for C_{max} and from 38.9 ng/mL*hr to 44.9 ng/mL*hr for AUC.

Trimethoprim: Co-administration of 160 mg trimethoprim and a single dose of 0.25 mg PRANDIN (after 2 days of twice daily and one dose on the third day of trimethoprim 160 mg) resulted in a 61% and 41% increase in repaglinide AUC and C_{max}, respectively. The increase in AUC was from 5.9 ng/mL*hr to 9.6 ng/mL*hr and the increase in C_{max} was from 4.7 ng/mL to 6.6 ng/mL.

Cyclosporine: Co-administration of 100 mg cyclosporine with a single dose of 0.25 mg repaglinide (after two 100 mg doses of cyclosporine twelve hours apart) increased the repaglinide (0.25 mg) C_{max} 1.8-fold and the AUC 2.5-fold in an interaction study with healthy volunteers (see **PRECAUTIONS**, Drug-Drug Interactions).

Rifampin: Co-administration of 600 mg rifampin and a single dose of 4 mg PRANDIN (after 6 days of once daily rifampin 600 mg) resulted in a 32% and 26% decrease in repaglinide AUC and C_{max}, respectively. The decreases were from 40.4 ng/mL to 29.7 ng/mL for C_{max}, and from 56.8 ng/mL*hr to 38.7 ng/mL*hr for AUC.

In another study, co-administration of 600 mg rifampin and a single dose of 4 mg PRANDIN (after 6 days of once daily rifampin 600 mg) resulted in a 48% and

17% decrease in repaglinide median AUC and median C_{max} respectively. The median decreases were from 54 ng/mL*hr to 28 ng/mL*hr for AUC and from 35 ng/mL to 29 ng/mL for C_{max}. PRANDIN administered by itself (after 7 days of once daily rifampin 600 mg) resulted in an 80% and 79% decrease in repaglinide median AUC and C_{max} respectively. The decreases were from 54 ng/mL*hr to 11 ng/mL*hr for AUC and from 35 ng/mL to 7.5 ng/mL for C_{max}.

Levonorgestrel & Ethinyl Estradiol: Co-administration of a combination tablet of 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol administered once daily for 21 days with 2 mg PRANDIN administered three times daily (days 1-4) and a single dose on Day 5 resulted in 20% increases in repaglinide, levonorgestrel, and ethinyl estradiol C_{max}. The increase in repaglinide C_{max} was from 40.5 ng/mL to 47.4 ng/mL. Ethinyl estradiol AUC parameters were incr ased by 20%, while repaglinide and levonorgestrel AUC values remained unchanged.

Simvastatin: Co-administration of 20 mg simvastatin and a single dose of 2 mg PRANDIN (after 4 days of once daily simvastatin 20 mg and three times daily PRANDIN 2 mg) resulted in a 26% increase in repaglinide C_{max} from 23.6 ng/mL to 29.7 ng/mL. AUC was unchanged.

Nifedipine: Co-administration of 10 mg nifedipine with a single dose of 2 mg PRANDIN (after 4 days of three times daily nifedipine 10 mg and three times daily PRANDIN 2 mg) resulted in unchanged AUC and C_{max} values for both drugs.

Clarithromycin: Co-administration of 250 mg clarithromycin and a single dose of 0.25 mg PRANDIN (after 4 days of twice daily clarithromycin 250 mg)

resulted in a 40% and 67% increase in repaglinide AUC and C_{max}, respectively. The increase in AUC was from 5.3 ng/mL*hr to 7.5 ng/mL*hr and the increase in C_{max} was from 4.4 ng/mL to 7.3 ng/mL.

Renal Insufficiency: Single-dose and steady-state pharmacokinetics of repaglinide were compared between patients with type 2 diabetes and normal renal function (CrCl > 80 mL/min), mild to moderate renal function impairment (CrCl = 40 – 80 mL/min), and severe renal function impairment (CrCl = 20 – 40 mL/min). Both AUC and C_{max} of repaglinide were similar in patients with normal and mild to moderately impaired renal function (mean values 56.7 ng/mL*hr vs 57.2 ng/mL*hr and 37.5 ng/mL vs 37.7 ng/mL, respectively.) Patients with severely reduced renal function had elevated mean AUC and C_{max} values (98.0 ng/mL*hr and 50.7 ng/mL, respectively), but this study showed only a weak correlation between repaglinide levels and creatinine clearance. Initial dose adjustment does not appear to be necessary for patients with mild to moderate renal dysfunction. **However, patients with type 2 diabetes who have *severe* renal function impairment should initiate PRANDIN therapy with the 0.5 mg dose – subsequently, patients should be carefully titrated. Studies were not conducted in patients with creatinine clearances below 20 mL/min or patients with renal failure requiring hemodialysis.**

Hepatic Insufficiency: A single-dose, open-label study was conducted in 12 healthy subjects and 12 patients with chronic liver disease (CLD) classified by Child-Pugh scale and caffeine clearance. Patients with moderate to severe impairment of liver function had higher and more prolonged serum concentrations

of both total and unbound repaglinide than healthy subjects ($AUC_{healthy}$: 91.6 ng/mL*hr; $AUC_{CLD\ patients}$: 368.9 ng/mL*hr; $C_{max,\ healthy}$: 46.7 ng/mL; $C_{max,\ CLD\ patients}$: 105.4 ng/mL). AUC was statistically correlated with caffeine clearance. No difference in glucose profiles was observed across patient groups. Patients with impaired liver function may be exposed to higher concentrations of repaglinide and its associated metabolites than would patients with normal liver function receiving usual doses. Therefore, **PRANDIN should be used cautiously in patients with impaired liver function. Longer intervals between dose adjustments should be utilized to allow full assessment of response.**

Clinical Trials

Monotherapy Trials

A four-week, double-blind, placebo-controlled dose-response trial was conducted in 138 patients with type 2 diabetes using doses ranging from 0.25 to 4 mg taken with each of three meals. PRANDIN therapy resulted in dose-proportional glucose lowering over the full dose range. Plasma insulin levels increased after meals and reverted toward baseline before the next meal. Most of the fasting blood glucose-lowering effect was demonstrated within 1-2 weeks.

In a double-blind, placebo-controlled, 3-month dose titration study, PRANDIN or placebo doses for each patient were increased weekly from 0.25 mg through 0.5, 1, and 2 mg, to a maximum of 4 mg, until a fasting plasma glucose (FPG) level <160 mg/dL was achieved or the maximum dose reached. The dose that achieved the targeted control or the maximum dose was continued to end of study. FPG and 2-hour post-prandial glucose (PPG) increased in patients re-

ceiving placebo and decreased in patients treated with repaglinide. Differences between the repaglinide and placebo-treated groups were -61 mg/dL (FPG) and -104 mg/dL (PPG). The between-group change in HbA_{1c}, which reflects long-term glycemic control, was 1.7% units.

PRANDIN vs. Placebo Treatment: Mean FPG, PPG, and HbA_{1c} Changes from baseline after 3 months of treatment:

	FPG (mg/dL)		PPG (mg/dL)		HbA_{1c} (%)	
	PL	R	PL	R	PL	R
Baseline	215.3	220.2	245.2	261.7	8.1	8.5
Change from Baseline (at last visit)	30.3	-31.0*	56.5	-47.6*	1.1	-0.6*

FPG = fasting plasma glucose
PPG = post-prandial glucose
PL = placebo (N=33)
R = repaglinide (N=66)
*: $p < 0.05$ for between group difference

Another double-blind, placebo-controlled trial was carried out in 362 patients treated for 24 weeks. The efficacy of 1 and 4 mg preprandial doses was demonstrated by lowering of fasting blood glucose and by HbA_{1c} at the end of the study. HbA_{1c}, for the PRANDIN-treated groups (1 and 4 mg groups combined) at the end of the study was decreased compared to the placebo-treated group in previously naïve patients and in patients previously treated with oral hypogly-

cemic agents by 2.1% units and 1.7% units, respectively. In this fixed-dose trial, patients who were naïve to oral hypoglycemic agent therapy and patients in relatively good glycemic control at baseline (HbA_{1c} below 8%) showed greater blood glucose-lowering including a higher frequency of hypoglycemia. Patients who were previously treated and who had baseline $HbA_{1c} \geq 8\%$ reported hypoglycemia at the same rate as patients randomized to placebo. There was no average gain in body weight when patients previously treated with oral hypoglycemic agents were switched to PRANDIN. The average weight gain in patients treated with PRANDIN and not previously treated with sulfonylurea drugs was 3.3%.

The dosing of PRANDIN relative to meal-related insulin release was studied in three trials including 58 patients. Glycemic control was maintained during a period in which the meal and dosing pattern was varied (2, 3 or 4 meals per day; before meals x 2, 3, or 4) compared with a period of 3 regular meals and 3 doses per day (before meals x 3). It was also shown that PRANDIN can be administered at the start of a meal, 15 minutes before, or 30 minutes before the meal with the same blood glucose-lowering effect.

PRANDIN was compared to other insulin secretagogues in 1-year controlled trials to demonstrate comparability of efficacy and safety. Hypoglycemia was reported in 16% of 1228 PRANDIN patients, 20% of 417 glyburide patients, and 19% of 81 glipizide patients. Of PRANDIN-treated patients with symptomatic hypoglycemia, none developed coma or required hospitalization.

Combination Trials

PRANDIN was studied in combination with metformin in 83 patients not satisfactorily controlled on exercise, diet, and metformin alone. PRANDIN dosage was titrated for 4 to 8 weeks, followed by a 3-month maintenance period. Combination therapy with PRANDIN and metformin resulted in significantly greater improvement in glycemic control as compared to repaglinide or metformin monotherapy. HbA_{1c} was improved by 1% unit and FPG decreased by an additional 35 mg/dL. In this study where metformin dosage was kept constant, the combination therapy of PRANDIN and metformin showed dose-sparing effects with respect to PRANDIN. The greater efficacy response of the combination group was achieved at a lower daily repaglinide dosage than in the PRANDIN monotherapy group (see Table).

PRANDIN and Metformin Therapy: Mean Changes from Baseline in Glycemic Parameters and Weight after 4 to 5 Months of Treatment[1]

	PRANDIN	Combination	Metformin
N	28	27	27
Median Final Dose (mg/day)	12	6 (PRANDIN) 1500 (metformin)	1500
HbA_{1c} (% units)	-0.38	-1.41*	-0.33
FPG (mg/dL)	8.8	-39.2 *	-4.5
Weight (kg)	3.0	2.4 #	-0.90

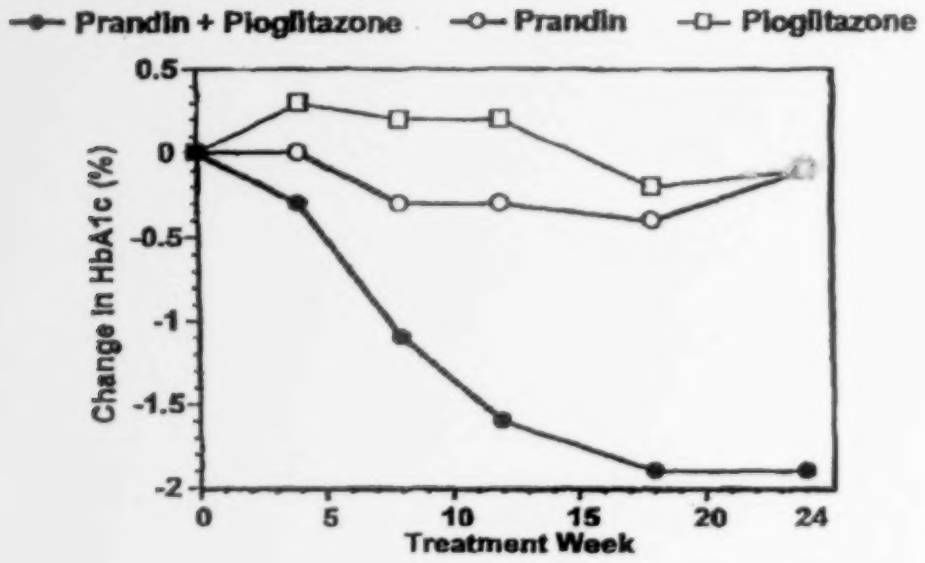
1: based on intent-to-treat analysis

*: $p < 0.05$, for pairwise comparisons with PRANDIN and metformin.

#: $p < 0.05$, for pairwise comparison with metformin.

A combination therapy regimen of PRANDIN and pioglitazone was compared to monotherapy with either agent alone in a 24-week trial that enrolled 246 patients previously treated with sulfonylurea or metformin monotherapy ($HbA_{1c} > 7.0\%$). Numbers of patients treated were: PRANDIN (N = 61), pioglitazone (N = 62), combination (N = 123). PRANDIN dosage was titrated during the first 12 weeks, followed by a 12-week maintenance period. Combination therapy resulted in significantly greater improvement in glycemic control as compared to monotherapy (figure below). The changes from baseline for completers in FPG (mg/dL) and HbA_{1c} (%), respectively were: -39.8 and -0.1 for PRANDIN, -35.3 and -0.1 for pioglitazone and -92.4 and -1.9 for the combination. In this study where pioglitazone dosage was kept constant, the combination therapy group showed dose-sparing effects with respect to PRANDIN (see figure legend). The greater efficacy response of the combination group was achieved at a lower daily repaglinide dosage than in the PRANDIN monotherapy group. Mean weight increases associated with combination, PRANDIN and pioglitazone therapy were 5.5 kg, 0.3 kg, and 2.0 kg respectively.

HbA_{1c} Values from PRANDIN / Pioglitazone Combination Study



HbA_{1c} values by study week for patients who completed study (combination, N = 101; PRANDIN, N = 35, pioglitazone, N = 26). Subjects with FPG above 270 mg/dL were withdrawn from the study. Pioglitazone dose: fixed at 30 mg/day; PRANDIN median final dose: 6 mg/day for combination and 10 mg/day for monotherapy.

A combination therapy regimen of PRANDIN and rosiglitazone was compared to monotherapy with either agent alone in a 24-week trial that enrolled 252 patients previously treated with sulfonylurea or metformin (HbA_{1c} > 7.0%). Combination therapy resulted in significantly greater improvement in glycemic control as compared to monotherapy (table below). The glycemic effects of the combination therapy were dose-sparing with respect to both total daily PRANDIN dosage and total daily rosiglitazone dosage (see table legend). A greater efficacy response of the combination therapy group was achieved with half the

median daily dose of PRANDIN and rosiglitazone, as compared to the respective monotherapy groups. Mean weight change associated with combination therapy was greater than that of PRANDIN monotherapy.

Mean Changes from Baseline in Glycemic Parameters and Weight in a 24-Week PRANDIN/Rosiglitazone Combination Study[1]

	PRANDIN	Combination	Rosiglitazone
N	63	127	62
HbA_{1c} (%)			
Baseline	9.3	9.1	9.0
Change by 24 weeks	-0.17	-1.43 *	-0.56
FPG (mg/dL)			
Baseline	269	257	252
Change by 24 weeks	-54	-94 *	-67
Change in Weight (kg)	+1.3	+4.5 #	+3.3

1: based on intent-to-treat analysis

*: p-value ≤ 0.001 for comparison to either monotherapy

#: p-value < 0.001 for comparison to PRANDIN
Final median doses: rosiglitazone - 4 mg/day for combination and 8 mg/day for monotherapy;
PRANDIN - 6 mg/day for combination and 12 mg/day for monotherapy

INDICATIONS AND USAGE

PRANDIN is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

CONTRAINDICATIONS

PRANDIN is contraindicated in patients with:

1. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
2. Type 1 diabetes.
3. Co-administration of gemfibrozil.
4. Known hypersensitivity to the drug or its inactive ingredients.

PRECAUTIONS

General: PRANDIN is not indicated for use in combination with NPH-insulin (See **ADVERSE REACTIONS, Cardiovascular Events**)

Macrovascular Outcomes:

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with PRANDIN or any other anti-diabetic drug.

Hypoglycemia: All oral blood glucose-lowering drugs including repaglinide are capable of producing hypoglycemia. Proper patient selection, dosage, and instructions to the patients are important to avoid hypoglycemic episodes. Hepatic insufficiency may

cause elevated repaglinide blood levels and may diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemia. Elderly, debilitated, or malnourished patients, and those with adrenal, pituitary, hepatic, or severe renal insufficiency may be particularly susceptible to the hypoglycemic action of glucose-lowering drugs.

Hypoglycemia may be difficult to recognize in the elderly and in people taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

The frequency of hypoglycemia is greater in patients with type 2 diabetes who have not been previously treated with oral blood glucose-lowering drugs (naïve) or whose HbA_{1c} is less than 8%. PRANDIN should be administered with meals to lessen the risk of hypoglycemia.

Loss of Control of Blood Glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of glycemic control may occur. At such times, it may be necessary to discontinue PRANDIN and administer insulin. The effectiveness of any hypoglycemic drug in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when the drug is first given. Adequate adjustment of dose and adhe-

rence to diet should be assessed before classifying a patient as a secondary failure.

Information for Patients

Patients should be informed of the potential risks and advantages of PRANDIN and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose and HbA_{1c}. The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development and concomitant administration of other glucose-lowering drugs should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Patients should be instructed to take PRANDIN before meals (2, 3, or 4 times a day preprandially). Doses are usually taken within 15 minutes of the meal but time may vary from immediately preceding the meal to as long as 30 minutes before the meal. **Patients who skip a meal (or add an extra meal) should be instructed to skip (or add) a dose for that meal.**

Laboratory Tests

Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels with a goal of decreasing these levels towards the normal range. During dose adjustment, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Glycosylated hemoglobin may be especially useful for evaluating long-term glycemic control. Postprandial glucose level testing may be clinically

helpful in patients whose pre-meal blood glucose levels are satisfactory but whose overall glycemic control (HbA_{1c}) is inadequate.

Drug-Drug Interactions

In vitro data indicate that PRANDIN is metabolized by cytochrome P450 enzymes 2C8 and 3A4. Consequently, repaglinide metabolism may be altered by drugs which influence these cytochrome P450 enzyme systems via induction and inhibition. Caution should therefore be used in patients who are on PRANDIN and taking inhibitors and/or inducers of CYP2C8 and CYP3A4. The effect may be very significant if both enzymes are inhibited at the same time resulting in a substantial increase in repaglinide plasma concentrations. Drugs that are known to inhibit CYP3A4 include antifungal agents like ketoconazole, itraconazole, and antibacterial agents like erythromycin. Drugs that are known to inhibit CYP2C8 include agents like trimethoprim, gemfibrozil and montelukast. Drugs that induce the CYP3A4 and/or 2C8 enzyme systems include rifampin, barbiturates, and carbamezapine. See **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions**.

Repaglinide appears to be a substrate for active hepatic uptake transporter (organic anion transporting protein OATP1B1). Drugs that inhibit OATP1B1 (e.g. cyclosporine) may likewise have the potential to increase plasma concentrations of repaglinide. See **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions**.

In vivo data from a study that evaluated the coadministration of a cytochrome P450 enzyme 3A4 inhibitor, clarithromycin, with PRANDIN resulted in a clinically significant increase in repaglinide plasma

levels. In addition, an increase in repaglinide plasma levels was observed in a study that evaluated the co-administration of PRANDIN with trimethoprim, a cytochrome P450 enzyme 2C8 inhibitor. These increases in repaglinide plasma levels may necessitate a PRANDIN dose adjustment. See **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions.**

Gemfibrozil significantly increased PRANDIN exposure. Therefore, patients should not take PRANDIN with gemfibrozil. See **CLINICAL PHARMACOLOGY** section, Drug-Drug Interactions, and **CONTRAINDICATIONS.**

The hypoglycemic action of oral blood glucose-lowering agents may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, cyclosporine, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving oral blood glucose-lowering agents, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving oral blood glucose-lowering agents, the patient should be observed closely for loss of glycemic control.

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When these drugs are administered to a patient receiving oral blood glucose-lowering agents, the

patient should be observed for loss of glycemic control. When these drugs are withdrawn from a patient receiving oral blood glucose-lowering agents, the patient should be observed closely for hypoglycemia.

Carcinogenesis, Mutagenesis, and Impairment Of Fertility

Long-term carcinogenicity studies were performed for 104 weeks at doses up to and including 120 mg/kg body weight/day (rats) and 500 mg/kg body weight/day (mice) or approximately 60 and 125 times clinical exposure, respectively, on a mg/m^2 basis. No evidence of carcinogenicity was found in mice or female rats. In male rats, there was an increased incidence of benign adenomas of the thyroid and liver. The relevance of these findings to humans is unclear. The no-effect doses for these observations in male rats were 30 mg/kg body weight/day for thyroid tumors and 60 mg/kg body weight/day for liver tumors, which are over 15 and 30 times, respectively, clinical exposure on a mg/m^2 basis.

Repaglinide was non-genotoxic in a battery of *in vivo* and *in vitro* studies: Bacterial mutagenesis (Ames test), *in vitro* forward cell mutation assay in V79 cells (HGPRT), *in vitro* chromosomal aberration assay in human lymphocytes, unscheduled and replicating DNA synthesis in rat liver, and *in vivo* mouse and rat micronucleus tests.

Fertility of male and female rats was unaffected by repaglinide administration at doses up to 80 mg/kg body weight/day (females) and 300 mg/kg body weight/day (males); over 40 times clinical exposure on a mg/m^2 basis.

Pregnancy

Pregnancy category C

Teratogenic Effects: Safety in pregnant women has not been established. Repaglinide was not teratogenic in rats or rabbits at doses 40 times (rats) and approximately 0.8 times (rabbit) clinical exposure (on a mg/m^2 basis) throughout pregnancy. Because animal reproduction studies are not always predictive of human response, PRANDIN should be used during pregnancy only if it is clearly needed.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Offspring of rat dams exposed to repaglinide at 15 times clinical exposure on a mg/m^2 basis during days 17 to 22 of gestation and during lactation developed nonteratogenic skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. This effect was not seen at doses up to 2.5 times clinical exposure (on a mg/m^2 basis) on days 1 to 22 of pregnancy or at higher doses given during days 1 to 16 of pregnancy. Relevant human exposure has not occurred to date and therefore the safety of PRANDIN administration throughout pregnancy or lactation cannot be established.

Nursing Mothers

In rat reproduction studies, measurable levels of repaglinide were detected in the breast milk of the dams and lowered blood glucose levels were observed

in the pups. Cross fostering studies indicated that skeletal changes (see **Nonteratogenic Effects**) could be induced in control pups nursed by treated dams, although this occurred to a lesser degree than those pups treated *in utero.* Although it is not known whether repaglinide is excreted in human milk some oral agents are known to be excreted by this route. Because the potential for hypoglycemia in nursing infants may exist, and because of the effects on nursing animals, a decision should be made as to whether PRANDIN should be discontinued in nursing mothers, or if mothers should discontinue nursing. If PRANDIN is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

No studies have been performed in pediatric patients.

Geriatric Use

In repaglinide clinical studies of 24 weeks or greater duration, 415 patients were over 65 years of age. In one-year, active-controlled trials, no differences were seen in effectiveness or adverse events between these subjects and those less than 65 other than the expected age-related increase in cardiovascular events observed for PRANDIN and comparator drugs. There was no increase in frequency or severity of hypoglycemia in older subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals to PRANDIN therapy cannot be ruled out.

ADVERSE REACTIONS

Hypoglycemia: See **PRECAUTIONS** and **OVERDOSAGE** sections.

PRANDIN has been administered to 2931 individuals during clinical trials. Approximately 1500 of these individuals with type 2 diabetes have been treated for at least 3 months, 1000 for at least 6 months, and 800 for at least 1 year. The majority of these individuals (1228) received PRANDIN in one of five 1-year, active-controlled trials. The comparator drugs in these 1-year trials were oral sulfonylurea drugs (SU) including glyburide and glipizide. Over one year, 13% of PRANDIN patients were discontinued due to adverse events, as were 14% of SU patients. The most common adverse events leading to withdrawal were hyperglycemia, hypoglycemia, and related symptoms (see **PRECAUTIONS**). Mild or moderate hypoglycemia occurred in 16% of PRANDIN patients, 20% of glyburide patients, and 19% of glipizide patients.

The table below lists common adverse events for PRANDIN patients compared to both placebo (in trials 12 to 24 weeks duration) and to glyburide and glipizide in one year trials. The adverse event profile of PRANDIN was generally comparable to that for sulfonylurea drugs (SU).

Commonly Reported Adverse Events (% of Patients)*

EVENT	PRANDIN N = 352	PLACEBO N = 108	PRANDIN N = 1228	SUN = 498
	Placebo controlled studies		Active controlled studies	
Metabolic				
Hypoglycemia	31**	7	16	20
Respiratory				
URI	16	8	10	10
Sinusitis	6	2	3	4
Rhinitis	3	3	7	8
Bronchitis	2	1	6	7
Gastrointestinal				
Nausea	5	5	3	2
Diarrhea	5	2	4	6
Constipation	3	2	2	3
Vomiting	3	3	2	1
Dyspepsia	2	2	4	2
Musculoskeletal				
Arthralgia	6	3	3	4
Back Pain	5	4	6	7
Other				
Headache	11	10	9	8
Paresthesia	3	3	2	1

Chest pain	3	1	2	1
Urinary tract infection	2	1	3	3
Tooth disorder	2	0	<1	<1
Allergy	2	0	1	<1

*: Events ≥2% for the PRANDIN group in the placebo-controlled studies and ≥ events in the placebo group

: See trial description in **CLINICAL PHARMACOLOGY, Clinical Trials

Cardiovascular Events

In one-year trials comparing PRANDIN to sulfonylurea drugs, the incidence of angina was comparable (1.8%) for both treatments, with an incidence of chest pain of 1.8% for PRANDIN and 1.0% for sulfonylureas. The incidence of other selected cardiovascular events (hypertension, abnormal EKG, myocardial infarction, arrhythmias, and palpitations) was ≤ 1% and not different between PRANDIN and the comparator drugs.

The incidence of total serious cardiovascular adverse events, including ischemia, was higher for repaglinide (4%) than for sulfonylurea drugs (3%) in controlled comparator clinical trials. In 1-year controlled trials, PRANDIN treatment was not associated with excess mortality when compared to the rates observed with other oral hypoglycemic agent therapies.

Summary of Serious Cardiovascular Events (% of total patients with events) in Trials Comparing PRANDIN to Sulfonylureas

	PRANDIN	SU*
Total Exposed	1228	498
Serious CV Events	4%	3%
Cardiac Ischemic Events	2%	2%
Deaths due to CV Events	0.5%	0.4%

*: glyburide and glipizide

Seven controlled clinical trials included PRANDIN combination therapy with NPH-insulin (n=431), insulin formulations alone (n=388) or other combinations (sulfonylurea plus NPH-insulin or PRANDIN plus metformin) (n=120). There were six serious adverse events of myocardial ischemia in patients treated with PRANDIN plus NPH-insulin from two studies, and one event in patients using insulin formulations alone from another study.

Infrequent Adverse Events (<1% of Patients)

Less common adverse clinical or laboratory events observed in clinical trials included elevated liver enzymes, thrombocytopenia, leukopenia, and anaphylactoid reactions.

Although no causal relationship with repaglinide has been established, postmarketing experience includes reports of the following rare adverse events: alopecia, hemolytic anemia, pancreatitis, Stevens-Johnson Syndrome, and severe hepatic dysfunction including jaundice and hepatitis.

Changes in blood glucose levels may result in blurred vision and visual disturbances, especially at the initi-

ation of treatment with hypoglycemic agents. These changes are usually transient.

Combination Therapy with Thiazolidinediones

During 24-week treatment clinical trials of PRANDIN-rosiglitazone or PRANDIN-pioglitazone combination therapy (a total of 250 patients in combination therapy), hypoglycemia (blood glucose < 50 mg/dL) occurred in 7% of combination therapy patients in comparison to 7% for PRANDIN monotherapy, and 2% for thiazolidinedione monotherapy.

Peripheral edema was reported in 12 out of 250 PRANDIN-thiazolidinedione combination therapy patients and 3 out of 124 thiazolidinedione monotherapy patients, with no cases reported in these trials for PRANDIN monotherapy. When corrected for dropout rates of the treatment groups, the percentage of patients having events of peripheral edema per 24 weeks of treatment were 5% for PRANDIN-thiazolidinedione combination therapy, and 4% for thiazolidinedione monotherapy. There were reports in 2 of 250 patients (0.8%) treated with PRANDIN-thiazolidinedione therapy of episodes of edema with congestive heart failure. Both patients had a prior history of coronary artery disease and recovered after treatment with diuretic agents. No comparable cases in the monotherapy treatment groups were reported.

Mean change in weight from baseline was +4.9 kg for PRANDIN-thiazolidinedione therapy. There were no patients on PRANDIN-thiazolidinedione combination therapy who had elevations of liver transaminases (defined as 3 times the upper limit of normal levels).

OVERDOSAGE

In a clinical trial, patients received increasing doses of PRANDIN up to 80 mg a day for 14 days. There were few adverse effects other than those associated with the intended effect of lowering blood glucose. Hypoglycemia did not occur when meals were given with these high doses. Hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring may continue until the physician is assured that the patient is out of danger. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery. There is no evidence that repaglinide is dialyzable using hemodialysis.

Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of type 2 diabetes with PRANDIN.

The patient's blood glucose should be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect second-

ary failure, i.e., loss of an adequate blood glucose-lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels are of value in monitoring the patient's longer term response to therapy.

Short-term administration of PRANDIN may be sufficient during periods of transient loss of control in patients usually well controlled on diet.

PRANDIN doses are usually taken within 15 minutes of the meal but time may vary from immediately preceding the meal to as long as 30 minutes before the meal.

Starting Dose

For patients not previously treated or whose HbA_{1c} is < 8%, the starting dose should be 0.5 mg with each meal. For patients previously treated with blood glucose-lowering drugs and whose HbA_{1c} is ≥ 8%, the initial dose is 1 or 2 mg with each meal preprandially (see previous paragraph).

Dose Adjustment

Dosing adjustments should be determined by blood glucose response, usually fasting blood glucose. Postprandial glucose levels testing may be clinically helpful in patients whose pre-meal blood glucose levels are satisfactory but whose overall glycemic control (HbA_{1c}) is inadequate. The preprandial dose should be doubled up to 4 mg with each meal until satisfactory blood glucose response is achieved. At least one week should elapse to assess response after each dose adjustment.

The recommended dose range is 0.5 mg to 4 mg taken with meals. PRANDIN may be dosed preprandially 2, 3, or 4 times a day in response to changes in the pa-

tient's meal pattern. The maximum recommended daily dose is 16 mg.

Patient Management

Long-term efficacy should be monitored by measurement of HbA_{1c} levels approximately every 3 months. Failure to follow an appropriate dosage regimen may precipitate hypoglycemia or hyperglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy including hypoglycemia. When hypoglycemia occurs in patients taking a combination of PRANDIN and a thiazolidinedione or PRANDIN and metformin, the dose of PRANDIN should be reduced.

Patients Receiving Other Oral Hypoglycemic Agents

When PRANDIN is used to replace therapy with other oral hypoglycemic agents, PRANDIN may be started on the day after the final dose is given. Patients should then be observed carefully for hypoglycemia due to potential overlapping of drug effects. When transferred from longer half-life sulfonylurea agents (e.g., chlorpropamide) to repaglinide, close monitoring may be indicated for up to one week or longer.

Combination Therapy

If PRANDIN monotherapy does not result in adequate glycemic control, metformin or a thiazolidinedione may be added. If metformin or thiazolidinedione monotherapy does not provide adequate control, PRANDIN may be added. The starting dose and dose adjustments for PRANDIN combination therapy is the same as for PRANDIN monotherapy. The dose

of each drug should be carefully adjusted to determine the minimal dose required to achieve the desired pharmacologic effect. Failure to do so could result in an increase in the incidence of hypoglycemic episodes. Appropriate monitoring of FPG and HbA_{1c} measurements should be used to ensure that the patient is not subjected to excessive drug exposure or increased probability of secondary drug failure.

HOW SUPPLIED

PRANDIN (repaglinide) tablets are supplied as unscored, biconvex tablets available in 0.5 mg (white), 1 mg (yellow) and 2 mg (peach) strengths. Tablets are embossed with the Novo Nordisk (Apis) bull symbol and colored to indicate strength.

0.5 mg tablets (white)	Bottles of 100	NDC	00169-0081-81
	Bottles of 500	NDC	00169-0081-82
	Bottles of 1000	NDC	00169-0081-83
1 mg tablets (yellow)	Bottles of 100	NDC	00169-0082-81
	Bottles of 500	NDC	00169-0082-82
	Bottles of 1000	NDC	00169-0082-83
2 mg tablets (peach)	Bottles of 100	NDC	00169-0084-81
	Bottles of 500	NDC	00169-0084-82
	Bottles of 1000	NDC	00169-0084-83

Do not store above 25° C (77° F).
Protect from moisture. Keep bottles tightly closed.
Dispense in tight containers with safety closures.

Licensed Under US Patent No. RE 37,035.

PRANDIN® is a registered trademark of Novo Nordisk A/S.

Manufactured in Germany for
Novo Nordisk Inc.
Princeton, NJ 08540
1-800-727-6500
www.novonordisk-us.com

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Date of Issue: July 14, 2008
Version: 8

PATENT & EXCLUSIVITY DRUG PRODUCT LIST - CUMULATIVE SUPPLEMENT 5 - May 2009

See List footnote for information regarding List content

APPL/PROD NO	PATENT NO	PATENT EXPIRATION DATE	PATENT CODES	PATENT DELIST REQUESTED	EXCLUSIVITY CODE(S)	EXCLUSIVITY EXPIRATION DATE
RASAGILINE MESYLATE - AZILECT						
021641 001	>A> 5453446	Feb 07, 2017	U-219			
RASAGILINE MESYLATE - AZILECT						
021641 002	>A> 5453446	Feb 07, 2017	U-219			
REMIFENTANIL HYDROCHLORIDE - ULTIVA						
020630 001	5019583	Jul 12, 2018	DS DP U-952			
	5019583*PED	Jan 12, 2011				
REMIFENTANIL HYDROCHLORIDE - ULTIVA						
020630 002	5019583	Jul 12, 2018	DS DP U-952			
	5019583*PED	Jan 12, 2011				
REMIFENTANIL HYDROCHLORIDE - ULTIVA						
020630 003	5019583	Jul 12, 2018	DS DP U-952			
	5019583*PED	Jan 12, 2011				
REPAGLINIDE - PRANDIN						
020741 001	6677358	Jun 12, 2018	DS DP U-968			
REPAGLINIDE - PRANDIN						
020741 002	6677358	Jun 12, 2018	DS DP U-968			
REPAGLINIDE - PRANDIN						
020741 003	6677358	Jun 12, 2018	DS DP U-968			
RISEDRONATE SODIUM - ACTONEL						
020835 001	5583122	Dec 10, 2013	U-222			
	5583122*PED	Jun 10, 2014				
	6096342	Nov 22, 2011				
	6096342*PED	May 22, 2012				
	6165513	Jun 10, 2018				
	6165513*PED	Dec 10, 2018				
RISEDRONATE SODIUM - ACTONEL						
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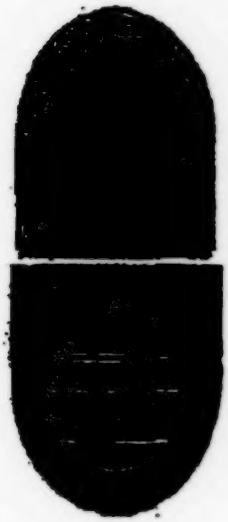
50



APPROVED DRUG PRODUCTS

WITH

THERAPEUTIC EQUIVALENCE EVALUATIONS

29th EDITION

THE PRODUCTS IN THIS LIST HAVE BEEN APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL SCIENCE
OFFICE OF GENERIC DRUGS

2009

NOVO-6901229

A1156

METFORMIN HYDROCHLORIDE

TABLET, EXTENDED RELEASE; ORAL

	GLUCOPHAGE XR					
AB	◆ BRISTOL MYERS SQUIBB	750MG		N021202	004	Apr 11, 2003
	METFORMIN HYDROCHLORIDE					
AB	ACTAVIS ELIZABETH	500MG		N076458	001	Oct 01, 2004
AB		750MG		N076878	001	Apr 13, 2005
AB	ANDRX PHARMS PT	500MG		N078394	001	Jun 07, 2006
AB		750MG		N078396	002	Jun 07, 2006
AB	APOTEX INC	500MG		N076706	001	Dec 14, 2004
AB		750MG		N076708	002	Dec 29, 2003
AB	BASF	750MG		N076453	001	Oct 14, 2004
AB	COBALT	500MG		N078038	001	Dec 14, 2004
AB	DIPAK LABS	500MG		N076345	001	Jul 30, 2004
AB		750MG		N076985	001	Sep 13, 2005
AB	IVAX PHARMS	500MG		N076545	001	Dec 01, 2003
AB	MYLAN	500MG		N076539	001	Sep 23, 2005
AB		750MG		N077333	001	Sep 08, 2005
AB	NEXGENRX INC	500MG		N076321	001	Apr 27, 2006
AB		750MG		N076322	002	Apr 27, 2006
AB	NORTHAM	500MG		N076734	001	Jul 26, 2006
AB	RANBAXY	500MG		N076433	001	Jun 18, 2004
AB		750MG		N077333	001	Jun 25, 2005
AB	SANDOZ	500MG		N076233	001	Dec 14, 2004
AB		750MG		N076872	001	Dec 14, 2004
AB	SUN PHARM INDS (IN)	500MG		N077336	001	Feb 09, 2006
AB		750MG		N077334	002	Feb 09, 2006
AB	TEVA	500MG		N076269	001	Jun 18, 2004
AB		750MG		N076864	002	Apr 12, 2005
AB	UNICHEM LABS FLORIDA	500MG		N076373	001	Jun 16, 2004
AB		750MG		N076969	001	Apr 12, 2005
AB	ZYDUS PHARMS USA	500MG		N077969	001	Apr 26, 2005
AB		750MG		N077974	001	Apr 21, 2005
	FORTAMET					
BX	ANDRX LABS LLC	500MG		N021574	001	Apr 27, 2004
BX	◆	1GM		N021574	002	Apr 27, 2004
	GLUMETZA					
BX	DEPOMED INC	500MG		N021748	001	Jun 03, 2005
BX	◆	1GM		N021748	002	Jun 03, 2005

METFORMIN HYDROCHLORIDE; PIOGLITAZONE HYDROCHLORIDE

TABLET; ORAL

	ACTOPLUS MET					
	TAKEDA GLOBAL	500MG;EQ 15MG BASE		N021842	001	Aug 29, 2005
	◆	850MG;EQ 15MG BASE		N021842	002	Aug 29, 2005

METFORMIN HYDROCHLORIDE; REPAGLINIDE

TABLET; ORAL

	PRANDIMET					
	NOVO NORDISK INC	500MG;1MG		N022105	001	Jun 23, 2008
	◆	500MG;2MG		N022105	002	Jun 23, 2008

METFORMIN HYDROCHLORIDE; ROSIGLITAZONE MALEATE

TABLET; ORAL

	AVANDAMET					
	GS PHARMCO	500MG;EQ 1MG BASE		N021410	001	Oct 10, 2002
		500MG;EQ 2MG BASE		N021410	002	Oct 10, 2002
		500MG;EQ 4MG BASE		N021410	003	Oct 10, 2002
		1GM;EQ 2MG BASE		N021410	004	Aug 25, 2003
	◆	1GM;EQ 4MG BASE		N021410	005	Aug 25, 2003

NOVO-6901230

PRESCRIPTION AND OTC DRUG PRODUCT PATENT AND EXCLUSIVITY LIST

See report footnote for information regarding report content

APPL/PROD NO	PATENT NO	PATENT EXPIRATION DATE	PATENT CODES	PATENT DELIST REQUESTED	EXCLUSIVITY CODE(S)	EXCLUSIVITY EXPIRATION DATE
METFORMIN HYDROCHLORIDE; PIOGLITAZONE HYDROCHLORIDE; ACTOPLUS MET						
021842 003	4687777	Jun 17, 2011	DS			
	5965584	Jun 19, 2016	DP U-679			
	6166042	Jun 19, 2016	U-679			
	6166043	Jun 19, 2016	U-679			
	6172890	Jun 19, 2016	U-679			
METFORMIN HYDROCHLORIDE; REPAGLINIDE; PRANDIMET						
022386 001	6677358	Jun 12, 2018	DP U-546			
	8837835	Mar 14, 2009	DS DP			
METFORMIN HYDROCHLORIDE; REPAGLINIDE; PRANDIMET						
022386 003	6677358	Jun 12, 2018	DP U-546			
	8837835	Mar 14, 2009	DS DP			
METFORMIN HYDROCHLORIDE; ROSIGLITAZONE MALEATE; AVANDAMET						
021410 001	5002953	Sep 17, 2011	DS DP U-493		I-494	May 19, 2009
	5002953	Sep 17, 2011	DS DP U-734		N-62	Jan 31, 2010
	5002953	Sep 17, 2011	DS DP U-691			
	5002953	Sep 17, 2011	DS DP U-690			
	5002953*PED	Mar 17, 2012				
	5741003	Apr 21, 2015	DS DP U-734	Y		
	5741003	Apr 21, 2015	DS DP U-493	Y		
	5741003*PED	Oct 21, 2015				
	5965584	Jun 19, 2016	U-493	Y		
	6166042	Jun 19, 2016	U-493	Y		
	6288095	Feb 11, 2017	U-493	Y		
	6288095*PED	Aug 11, 2017				
	7358366	Apr 19, 2020	DS			
	7358366*PED	Oct 19, 2020				
METFORMIN HYDROCHLORIDE; ROSIGLITAZONE MALEATE; AVANDAMET						
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	5741003	Apr 21, 2015	DS DP U-734	Y		
	5741003*PED	Oct 21, 2015				
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	6166042	Jun 19, 2016	U-493	Y		
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	7358366*PED	Oct 19, 2020				
METFORMIN HYDROCHLORIDE; ROSIGLITAZONE MALEATE; AVANDAMET						
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	5741003	Apr 21, 2015	DS DP U-734	Y		
	5741003*PED	Oct 21, 2015				
	5965584	Jun 19, 2016	U-493	Y		
	6166042	Jun 19, 2016	U-493	Y		
	6288095	Feb 11, 2017	U-493	Y		
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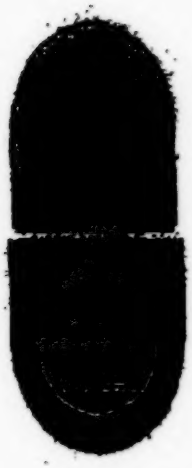
	7358366*PED	Oct 19, 2020				

NOVO-6901231

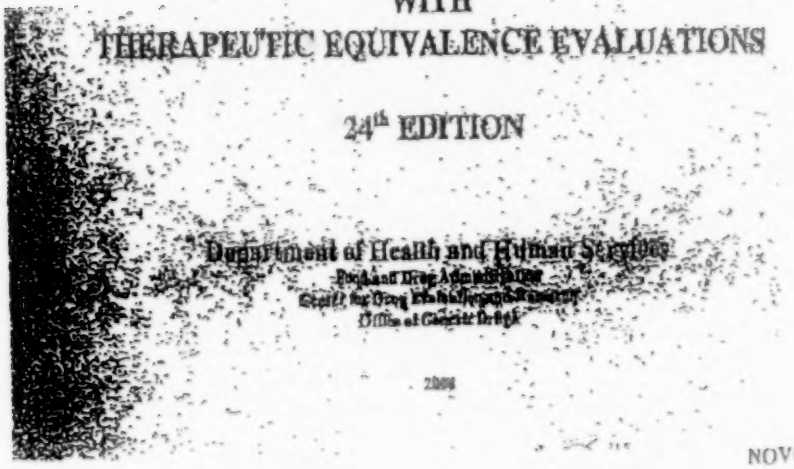
CUMULATIVE
SUPPLEMENT 12
DECEMBER 2004



APPROVED DRUG PRODUCTS

WITH
THERAPEUTIC EQUIVALENCE EVALUATIONS

24th EDITION



NOVO-6901272

PRESCRIPTION AND OTC DRUG PRODUCT
PATENT AND EXCLUSIVITY DATA
See report footnotes for information regarding report content

	APPL/PROD NUMBER	INGREDIENT NAME; TRADE NAME	PATENT NUMBER	PATENT/RED EXCL EXPIRES	PATENT CODE(S)	EXCLUS CODE	EXCLUS EXPIRES
	021073 001	PIOGLITAZONE HYDROCHLORIDE;ACTOS				M-35	NOV 26, 2006
	021073 002	PIOGLITAZONE HYDROCHLORIDE;ACTOS				M-35	NOV 26, 2006
	021073 003	PIOGLITAZONE HYDROCHLORIDE;ACTOS				M-35	NOV 26, 2006
>ADD>	021446 001	PREGABALIN;LYRICA				NCE	DEC 30, 2009
>ADD>	021446 002	PREGABALIN;LYRICA				NCE	DEC 30, 2009
>ADD>	021446 003	PREGABALIN;LYRICA				NCE	DEC 30, 2009
>ADD>	021446 004	PREGABALIN;LYRICA				NCE	DEC 30, 2009
>ADD>	021446 005	PREGABALIN;LYRICA				NCE	DEC 30, 2009
>ADD>	021446 006	PREGABALIN;LYRICA				NCE	DEC 30, 2009
>ADD>	021446 007	PREGABALIN;LYRICA				NCE	DEC 30, 2009
>ADD>	021446 008	PREGABALIN;LYRICA				NCE	DEC 30, 2009
	020639 001	QUETIAPINE FUMARATE;SEROQUEL	4879288	SEP 26, 2011	DS DP U550	I-419	JAN 12, 2007
						I-418	JAN 12, 2007
	020639 002	QUETIAPINE FUMARATE;SEROQUEL	4879288	SEP 26, 2011	DS DP U550	I-419	JAN 12, 2007
						I-418	JAN 12, 2007
	020639 003	QUETIAPINE FUMARATE;SEROQUEL	4879288	SEP 26, 2011	DS DP U550	I-419	JAN 12, 2007
						I-418	JAN 12, 2007
	020639 004	QUETIAPINE FUMARATE;SEROQUEL	4879288	SEP 26, 2011	DS DP U550	I-419	JAN 12, 2007
						I-418	JAN 12, 2007
	020639 005	QUETIAPINE FUMARATE;SEROQUEL	4879288	SEP 26, 2011	DS DP U550	I-419	JAN 12, 2007
						I-418	JAN 12, 2007
	020815 001	RALOXIFENE HYDROCHLORIDE;EVISTA	6797719	MAR 10, 2017	DP		
	021698 001	RANOLAZINE HYDROCHLORIDE;RANEXA 150				NP	AUG 31, 2007
	020741 001	REPAGLINIDE;PRANDIN	6677358	JUN 12, 2018	DS DP U546		
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	020303 002	RIMANTADIN;RIMANTADIN	6177874	NOV 01, 2016	U454		
			6177874*PED	MAY 01, 2017	U454		
			6461605	NOV 01, 2016	U478		
			6461605*PED	MAY 01, 2017	U478		
			6472373	SEP 21, 2017	U479		
			6472373*PED	MAR 21, 2018	U479		
			6524570	NOV 01, 2016	U499		
			6524570*PED	MAY 01, 2017	U499		
	076203 001	RIMANTADIN;RIMASEMIDE				PC	OCT 03, 2004
	076192 001	RIMANTADIN;RIMANTADIN				PC	OCT 03, 2004
	021361 001	RIPAXIDIN;RIPAXIDIN				NCE	MAY 25, 2009
	020035 003	RISEDRONATE SODIUM;ACTONEL	6465443	AUG 14, 2018	DP		
			6432932	JUL 17, 2018	U505		
	020659 001	RITONAVIR;NORVIR	6703403	JUN 26, 2016	U564		
	020945 001	RITONAVIR;NORVIR	6703403	JUN 26, 2016	U564		
	021042 001	RIPHOXIDIN;VIDIX	5474995	JUN 24, 2013	DS DP U602	NCE	MAY 20, 2004
			5691374	MAY 18, 2015		I-353	APR 11, 2005
			6063811	MAY 06, 2017	U602	M-27	AUG 06, 2006
			6239173	JUN 24, 2013	DS DP U602	PED	NOV 20, 2004
			5474995*PED	DEC 24, 2013		PED	OCT 11, 2005
			5691374*PED	NOV 18, 2015		PED	FEB 06, 2007
			6063811*PED	NOV 06, 2017		I-423	MAR 26, 2007
			6239173*PED	DEC 24, 2013			
	021042 002	RIPHOXIDIN;VIDIX	5474995	JUN 24, 2013	DS DP U602	NCE	MAY 20, 2004
			5691374	MAY 18, 2015		I-353	APR 11, 2005
			6063811	MAY 06, 2017	U602	M-27	AUG 06, 2006
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			5691374*PED	NOV 18, 2015		PED	FEB 06, 2007
			6063811*PED	NOV 06, 2017		I-423	MAR 26, 2007

NOVO-6901273

I-429 FOR USE IN COMBINATION WITH PREDNISONE FOR THE TREATMENT OF PATIENTS WITH ANDROGEN INDEPENDENT (HORMONE REFRACTORY) METASTATIC PROSTATE CANCER

I-430 FOR USE IN THE RELIEF OF THE SIGNS AND SYMPTOMS OF RHEUMATOID ARTHRITIS IN ADULTS

I-431 NOSOCOMIAL PNEUMONIA AND COMMUNITY-ACQUIRED PNEUMONIA CAUSED BY STREPTOCOCCUS PNEUMONIAE (INCLUDING COMBINED TRINCHOMEDICAL DRUG RESISTANT STRAINS

I-432 TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA CAUSED BY MULTI-DRUG RESISTANT STREPTOCOCCUS PNEUMONIAE

I-433 TREATMENT OF BIOPSY-CONFIRMED, PRIMARY SUPERFICIAL BASAL CELL CARCINOMA IN IMMUNOCOMPETENT ADULTS, WITH A MAXIMUM TUMOR DIAMETER OF 2.0CM, LOCATED ON THE TRUNK (EXCLUDING ANOGENITAL REGION), NECK, OR EXTREMITIES (EXCLUDING HANDS AND FEET)

I-434 PREVENTION OF CARDIOVASCULAR DISEASE IN ADULT PATIENTS WITHOUT CLINICALLY EVIDENT HEART DISEASE, BUT WITH MULTIPLE RISK FACTORS FOR CORONARY HEART DISEASE TO REDUCE RISK OF MI AND RISK OF REVASCULARIZATION PROCEDURES AND ANGINA

I-435 CHRONIC IDIOPATHIC CONSTIPATION

I-436 FOR USE IN COMBINATION WITH DOXORUBICIN AND CYCLOPHOSPHAMIDE FOR THE ADJUVANT TREATMENT OF PATIENTS WITH OPERABLE NODE-POSITIVE BREAST CANCER

I-437 TREATMENT OF ACUTE MANIC AND MIXED EPISODES ASSOCIATED WITH BIPOLAR DISORDER

I-438 EMPIRICAL THERAPY FOR PRESUMED FUNGAL INFECTIONS IN FEBRILE, NEUTROPENIC PATIENTS

I-439 USED TO TREAT ADULTS WITH GROWTH HORMONE DEFICIENCY

I-440 FOR THE REPLACEMENT OF ENDOGENOUS GROWTH HORMONE IN ADULTS WITH GROWTH HORMONE DEFICIENCY

I-441 USE COMBINATION WITH 5FU/LEUCOVORIN FOR ADJUVANT TREATMENT STAGE III COLON CANCER PTS WHO HAVE UNDERGONE COMPLETE RESECTION PRIMARY TUMOR BASED ON IMPROVEMENT IN DISEASE FREE SURVIVAL, NO DEMONSTRATED BENEFIT OVERALL SURVIVAL AFTER 4YRS

I-442 USED FOR CANDIDEMIA IN NONNEUTROPENIC PATIENTS AND THE FOLLOWING CANDIDA INFECTIONS: DISSEMINATED INFECTIONS IN SKIN & INFECTIONS IN ABDOMEN, KIDNEY, BLADDER WALL, AND

I-443 TREATMENT OF NASAL POLYPS IN PATIENTS 18 YEARS OF AGE AND OLDER

I-444 USE OF PROTONIX IV FOR INJECTION AS STAND ALONE THERAPY FOR THE SHORT-TERM TREATMENT OF PATIENTS HAVING GASTROESOPHAGEAL REFLUX (GERD) WITH A HISTORY OF EROSIVE

I-445 TO IMPROVE (COMPARED TO 4.25% DEXTROSE) ULTRAFILTRATION AND CLEARANCE OF CREATININE AND UREA NITROGEN IN PATIENTS WITH HIGH AVERAGE OR GREATER TRANSPORT CHARACTERISTICS, AS DEFINED USING THE PERITONEAL EQUILIBRATION TEST (PET)

EXCLUSIVITY MISCELLANEOUS

M-30 CHANGES TO CLINICAL PHARMACOLOGY, PRECAUTIONS, AND DOSAGE AND ADMINISTRATION SECTIONS OF LABELING CONCERNING USE OF LOTENSIN IN PEDIATRIC PATIENTS WITH HYPERTENSION

M-31 INFORMATION FOR USE IN PEDIATRIC PATIENTS WITH CHRONIC KIDNEY DISEASE STAGE 5 (END-STAGE RENAL DISEASE)

M-32 ADDITIONAL LANGUAGE TO CLINICAL PHARMACOLOGY AND CLINICAL STUDIES

M-33 INFORMATION FOR USE OF ADVAIR DISKUS 100/50 IN CHILDREN 4 TO 11 YEARS OF AGE WITH ASTHMA

M-34 EXPANDED INFORMATION TO PEDIATRIC USE SUBSECTION OF LABELING IN RESPONSE TO PEDIATRIC WRITTEN REQUEST

M-35 ADDITIONAL INFORMATION REGARDING CLINICAL STUDIES DONE WITH ACTOS-XR COMBINATION WITH METFORMIN, A SULFONYLUREA, OR INSULIN ADDED TO CLINICAL PHARMACOLOGY

M-36 ADDITION OF INFORMATION TO CLINICAL STUDIES REGARDING PREVENTION OF CARDIOVASCULAR DISEASE

M-37 INFORMATION ADDED TO THE LABELING THAT DETAILS INFORMATION RELATIVE TO STUDIES DONE IN PEDIATRIC POPULATIONS IN THE CLINICAL PHARMACOLOGY AND PEDIATRIC USE SUBSECTIONS

M-38 SAFETY AND BP-LOWERING EFFECTS OF TRUSOPT HAVE BEEN DEMONSTRATED IN PEDIATRIC PATIENTS IN A 3 MONTH, MULTI-CENTER DOUBLE-MASKED ACTIVE-TREATMENT-CONTROLLED TRIAL

M-39 FOR LABELING CHANGES BASED ON RESULTS OF THE SPD422-202 CLINICAL STUDY REPORT (CSR) SUBMITTED IN RESPONSE TO THE WRITTEN REQUEST

PATENT USE

U-546 USE OF REPAGLINIDE IN COMBINATION WITH METFORMIN TO LOWER BLOOD GLUCOSE

U-547 MAINTENANCE MONOTHERAPY FOR BIPOLAR DISORDER

U-548 A METHOD OF REDUCING FLUSHING IN AN INDIVIDUAL BEING TREATED FOR A LIPIDEMIC DISORDER AND EFFECTIVELY TREATING THE LIPIDEMIC DISORDER

U-549 USE IN THE TREATMENT OF MEN WITH ADVANCED HORMONE REFRACTORY PROSTATE CANCER

U-550 TREATMENT OF BIPOLAR MANIA AND SCHIZOPHRENIA

U-551 METHOD FOR REDUCING TOXICITY OF ACIVICIN TREATED PATIENTS BY ADMINISTERING FOLIC ACID

U-552 TREATMENT OF HYPERTENSION AND HYPERLIPIDEMIA WITH A SINGLE COMPOSITION

Orange Book Detail Record Search

Search results from the "OB_Rx" table for query on "020741."

Active Ingredient:	REPAGLINIDE
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	PRANDIN
Applicant:	NOVO NORDISK INC
Strength:	0.5MG
Application Number:	020741
Product Number:	001
Approval Date:	Dec 22, 1997
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: View

Active Ingredient:	REPAGLINIDE
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	PRANDIN
Applicant:	NOVO NORDISK INC
Strength:	1MG
Application Number:	020741
Product Number:	002
Approval Date:	Dec 22, 1997
Reference Listed Drug	No
RX/OTC/DISCN:	RX

TE Code:

Patent and Exclusivity Info for this product: View

Active Ingredient:	REPAGLINIDE
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	PRANDIN
Applicant:	NOVO NORDISK INC
Strength:	2MG
Application Number:	020741
Product Number:	003
Approval Date:	Dec 22, 1997
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX

TE Code:

Patent and Exclusivity Info for this product: View

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FDA/Center for Drug Evaluation and Research

Office of Generic Drugs

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Update Frequency:

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Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through April, 2009

Patent and Generic Drug Product Data Last Updated: June 05, 2009

Patent and Exclusivity Search Results from query on Appl No 020741 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent use Code	Delist Requested
020741	001	6677358	Jun 12, 2018	Y	Y	U-968	
020741	001	RE37035	Mar 14, 2009				

Exclusivity Data

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CRF 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

View a list of all patent use codes

View a list of all exclusivity codes

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Update Frequency:

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Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through April, 2009

Patent and Generic Drug Product Data Last Updated: June 05, 2009

Patent Use Codes

This page defines the patent use codes.

Code	**Definition**
U-968	A METHOD FOR IMPROVING GLYCEMIC CONTROL IN ADULTS WITH TYPE 2 DIABETES MELLITUS

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Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through April, 2009

Patent and Generic Drug Product Data Last Updated: June 05, 2009

http://www.accessdata.fda.gov/scripts/cder/ob/docs/
* * * * 6/8/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-741

December 22, 1997

RECEIVED
JAN 2 1998
BARRY REIT

Novo Nordisk Pharmaceuticals Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
100 Overlook Center, Suite 200
Princeton, NJ 08540-7810

Dear Dr. Reit:

Please refer to your new drug application dated June 27, 1997, received July 1, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prandin™ (repaglinide) 0.5 mg, 1 mg, and 2 mg Tablets.

We acknowledge receipt of your submissions dated August 14, 20, 26, and 27, September 2, 8, and 17, October 3, 14, 16, and 23, and December 12, 17, 18, and 22 (fax), 1997. The User Fee goal date for this application is January 1, 1998.

This new drug application provides for the use of Prandin™ Tablets as an adjunct to diet and exercise to lower blood glucose in patients with non-insulin dependent (type II) diabetes mellitus whose hyperglycemia cannot be controlled satisfactorily with diet and exercise alone. It also provides for the use of Prandin™ Tablets in combination with metformin to lower blood glucose in patients whose hyperglycemia cannot be con-

trolled by exercise, diet, and either repaglinide or metformin alone.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted (fax) on December 22, 1997, and the draft carton and container labeling dated June 27 and October 16, 1997. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-741. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submissions dated December 22 (fax), 1997. These commitments are listed below.

1. A long-term, simplified clinical trial to assess further the long-term safety, including the incidence of cardiovascular events, in patients with type 2 diabetes treated with Prandin™, a long acting sulfo-

nylurea drug, and other established therapy.

2. A clinical trial to assess efficacy in patients with type 2 diabetes and renal dysfunction.

3. Normal volunteer studies to document pharmacokinetic drug interactions with statins, estrogen, and calcium channel blockers.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii), we request a status summary of each commitment in your annual report to this application. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments should be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing,
Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the

Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Michael F. Johnston, R.Ph., Regulatory Management Officer, at (301) 827-6423.

Sincerely yours,

/s/ James Bilstad
James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

* * * *

[Copy of Correspondence Page Omitted]

US006677358B1

(12) United States Patent
Müller
(10) Patent No.: US 6,677,358 B1
(45) Date of Patent: Jan. 13, 2004

(54) NIDDM REGIMEN

(75) Inventor: Peter Giørtz Müller, Princeton Junction, NJ (US)

(73) Assignee: Novo Nordisk A/S, Bagsvaerd (DK)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 09/459,526

(22) Filed: Dec. 13, 1999

Related U.S. Application Data

(63) Continuation of application No. PCT/DK98/00248, filed on Jun. 12, 1998.

(60) Provisional application No. 60/063,368, filed on Oct. 29, 1997.

(30) Foreign Application Priority Data

Jun. 13, 1997 (DK) 0694/97

(51) Int. Cl.[7] A61K 31/155; A61K 31/4453; A61K 31/451

(52) U.S. Cl. 514/331; 514/635

(58) Field of Search 514/331, 635, 514/563

(56) References Cited

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(List continued on next page.)

Primary Examiner—Phyllis G. Spivack

(74) *Attorney, Agent, or Firm*—Reza Green, Esq.; Richard N. Boak, Esq.; Marc A. Began, Esq.

(57) **ABSTRACT**

The present invention discloses a regimen for the treatment of type 2 diabetes, in which the endogenous secretion of insulin is stimulated in connection with meals, by administering a short-acting, oral hypoglycemic agent. Also, the present invention discloses a method of achieving improvement in glycemic control by combined use of repaglinide and metformin in NIDDM patients poorly controlled on metformin alone.

5 Claims, 4 Drawing Sheets

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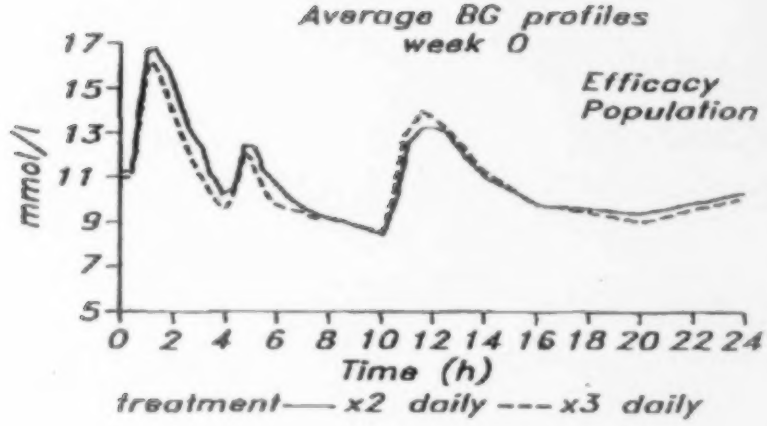

Average BG profiles
week 0
Efficacy
Population
mmol/l
17
15
13
11
9
7
5
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (h)
treatment—— x2 daily --- x3 daily

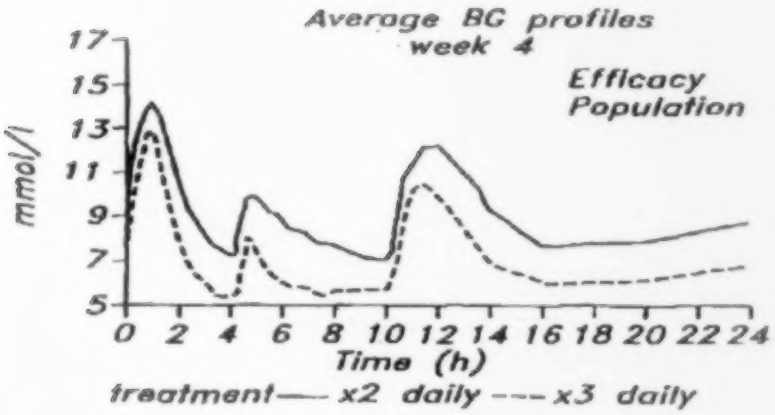

Average BG profiles
week 4
Efficacy
Population
mmol/l
17
15
13
11
9
7
5
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (h)
treatment—— x2 daily --- x3 daily

FIG 1

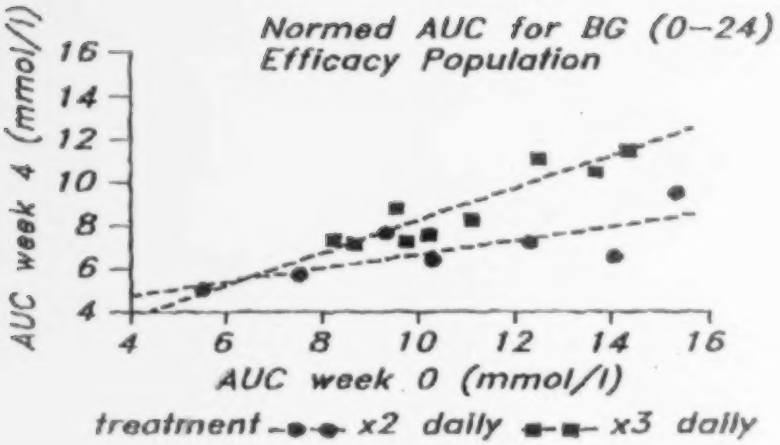

Normed AUC for BG (0–24)
Efficacy Population
AUC week 4 (mmol/l)
16
14
12
10
8
6
4
4
6
8
10
12
14
16
AUC week 0 (mmol/l)
treatment x2 daily x3 daily

FIG 2

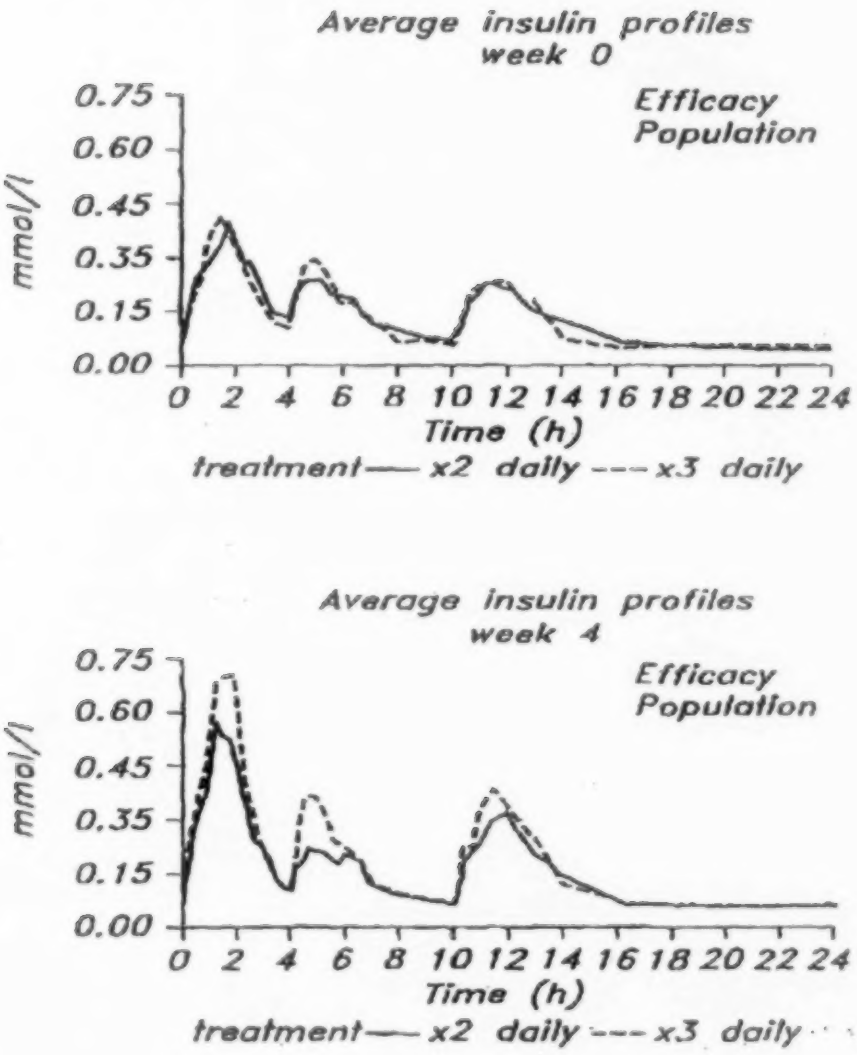

Average insulin profiles
week 0
Efficacy
Population
mmol/l
0.75
0.60
0.45
0.35
0.15
0.00
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (h)
treatment — x2 daily --- x3 daily
Average insulin profiles
week 4
Efficacy
Population
mmol/l
0.75
0.60
0.45
0.35
0.15
0.00
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (h)
treatment — x2 daily --- x3 daily

FIG 3

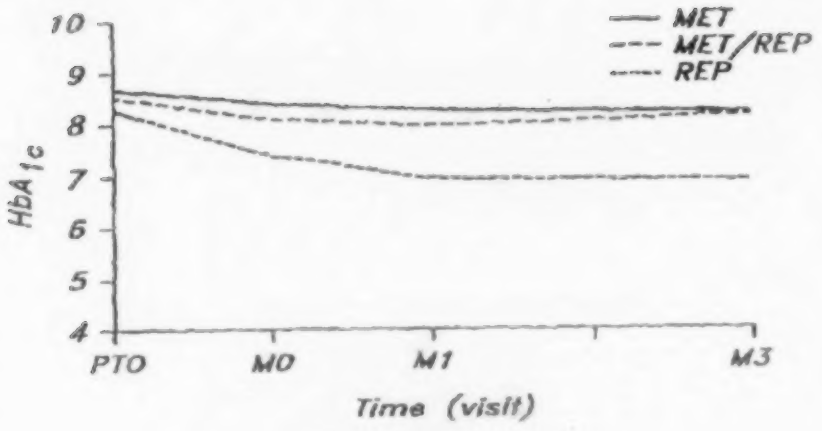


FIG 4

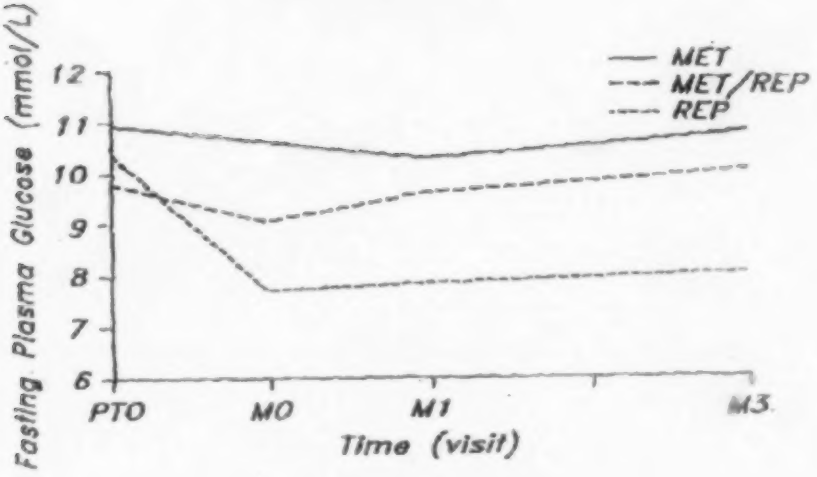


FIG 5

NIDDM REGIMEN

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of PCT/DK98/00248 filed on Jun. 12, 1998 and claims priority under 35 U.S.C. 119 of Danish application

no. 0694/97 filed on Jun. 13, 1997 and U.S. provisional application No. 60/063,368 filed on Oct. 29, 1997, the contents of which are fully incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to the use of a short-acting oral hypoglycemic agent and to a novel regimen in the treatment of type 2 diabetes in which the endogenous secretion of insulin is stimulated in connection with meals by administering in connection with the meals a short-acting oral hypoglycaemic agent. Also, the present invention relates to a method of achieving significantly improvement in the glycaemic control by a combined use of repaglinide and metformin in NIDDM patients poorly controlled on metformin alone.

BACKGROUND OF THE INVENTION

Diabetes is characterised by an impaired glucose metabolism manifesting itself among other things by an elevated blood glucose level in untreated diabetic patients. The underlying defects lead to a classification of diabetes into two major groups: type 1 diabetes, or insulin dependent diabetes mellitus (IDDM), which arises when patients lack ß-cells producing insulin in their pancreatic glands, and type 2 diabetes, or non-insulin dependent diabetes mellitus (NIDDM), which occurs in patients with an impaired ß-cell function besides a range of other abnormalities.

Type 1 diabetic patients are currently treated with insulin, while the majority of type 2 diabetic patients are treated either with agents that stimulate ß-cell function or with agents that enhance the tissue sensitivity of the patients towards insulin. Since the agents that stimulate ß-cell function or enhance the

tissue sensitivity of the patients towards insulin are typically administered orally, these agents arc collectively referred to as oral hypoglycemic agents or OHAs.

Among the agents applied for stimulation of the ß-cell function, those acting on the ATP-dependent potassium channel of ß-cells are most widely used in current therapy. The so-called sulphonylureas such as tolbutamide, glibenclamide, glipizide, and gliclazide are used extensively and other agents such as repaglinide also acting at this molecular site are under development. Repaglinide is (S)-(+)-2-ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl] amino]-2-oxo-ethyl]benzoic acid, a compound described i.a. in European patent application publication No. 0 589 874 (to Dr. Karl Thomae GmbH). Among the agents applied to enhance tissue sensitivity towards insulin, metformin is a representative example.

Even though sulphonylureas are widely used in the treatment of NIDDM this therapy is, in most instances, not satisfactory: In a large number of NIDDM patients sulphonylureas do not suffice to normalise blood sugar levels and the patients are, therefore, at high risk for acquiring diabetic complications. Also, many patients gradually lose the ability to respond to treatment with sulphonylureas and are thus gradually forced into insulin treatment. This shift of patients from oral hypoglycaemic agents to insulin therapy is usually ascribed to exhaustion of the ß-cells in NIDDM patients.

Over the years, numerous attempts have therefore been made to provide novel agents which stimulate ß-cell function in order to offer the NIDDM patients an improved treatment.

SUMMARY OF THE INVENTION

In one preferred aspect, the present invention relates to the use of a short-acting hypoglycemic agent capable of stimulating insulin secretion from ß-cells for the manufacture of a medicament adapted to stimulate prandial insulin secretion for the treatment of postprandial hyperglycemia in NIDDM.

In another preferred aspect, the present invention relates to the use of repaglinide for the manufacture of a medicament adapted to stimulate prandial insulin secretion for the treatment of postprandial hyperglycemia in NIDDM.

In another preferred aspect, the present invention relates to the use of A-4166 for the manufacture of a medicament adapted to stimulate prandial insulin secretion for the treatment of postprandial hyperglycemia in NIDDM (A4166 is N-[(trans-4-isopropylcyclohexyl)carbonyl]-D-phenylalanine (Shinkai H et al. J Med Chem 32: 1436-1441)).

In another preferred aspect, the present invention relates to the use of gliquidone for the manufacture of a medicament adapted to stimulate prandial insulin secretion for the treatment of postprandial hyperglycemia in NIDDM.

In another preferred aspect, the present invention relates to a method of treating NIDDM which comprises stimulating the insulin secretion in connection with a meal by administering prandially to a patient in need of such a treatment an effective amount of a short-acting hypoglycemic agent.

In another preferred aspect, the present invention relates to a method of treating NIDDM which comprises stimulating the insulin secretion in connection

with a meal by administering prandially to a patient in need of such a treatment an effective amount of repaglinide.

In another preferred aspect, the present invention relates to a method of treating NIDDM which comprises stimulating the insulin secretion in connection with a meal by administering prandially to a patient in need of such a treatment an effective amount of A-4166.

In another preferred aspect, the present invention relates to a method of treating NIDDM which comprises stimulating the insulin secretion in connection with a meal by administering prandially to a patient in need of such a treatment an effective amount of gliquidone.

In another preferred aspect, the present invention relates to a pharmaceutical kit suitable for use in achieving improved glycaemic control in NIDDM patients, the kit comprising an amount of repaglinide formulated for administration to a NIDDM patient; and a synergistically effective amount of metformin, formulated for administration to the NIDDM patient.

In a further preferred aspect, the present invention relates to a method of treating NIDDM which comprises stimulating the insulin secretion in connection with a meal by administering prandially to a patient in need of such a treatment an effective amount of a short-acting hypoglycemic agent supplemented with administration of a long-acting hypoglycemic agent. The long-acting hypoglycemic agent can be administered once per day or divided in sub-doses, preferably two or three sub-doses. Such a regimen may be useful in cases where the patient's basal insulin level is lower than desirable. A preferred short-

acting hypoglycemic agent for use in such a regimen is selected from the group comprising repaglinide, gliquidone and A-4166. A preferred long-acting hypoglycemic agent for use in such a regimen is selected from the group comprising metformin, chlorpropamide, tolbutamide, glibenclamide, glibornuride, gliclazide, glipizide and troglitazone.

Surprisingly, it has been found that when repaglinide is administered together with metformin to NIDDM patients whose glycemic control is poor on metformin alone a significant improvement in the glycaemic control is observed. More particularly, it has been found that there is a synergism between repaglinide and metformin. Thus, in a further preferred aspect, the present invention relates to a method of achieving improved glycemic control in NIDDM patients which comprises administering to a patient in need of such a treatment, an effective amount of repaglinide in a regimen which further comprises treatment with metformin.

In a further preferred aspect, the present invention relates to a pharmaceutical composition which comprises repaglinide and metformin together with a suitable carrier. In one preferred aspect, such a pharmaceutical composition is provided in the form of a tablet. In another preferred aspect, such a pharmaceutical composition is provided in the form of a capsule. Said composition preferably contains from about 0.01 mg to about 8 mg of repaglinide, more preferred from about 0.5 mg to about 6 mg of repaglinide and from about 50 mg to about 1500 mg, preferably from about 100 mg to about 1200 mg of metformin per dose unit.

In the present text, the term "a short-acting hypoglycemic agent" is used to designate a hypoglycemic agent with which maximum secretion of insulin is attained within 1 hour, preferably within 30 min. after administration of the agent, most preferred within 20 min. and which furthermore has a biological half-life, $T_{1/2}$, of less than 2 hours, preferably less than 1.5 hours. The term "a long-acting hypoglycemic agent" is used to designate a hypoglycemic agent with which maximum secretion of insulin is attained more than 1 hour after administration of the agent.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention is further illustrated with reference to the drawings wherein

FIG. 1 shows mean blood glucose profiles at baseline and week 4.

FIG. 2 shows normed AUC for blood glucose (0-24) after 4 weeks versus normed AUC for blood glucose (0-24) at baseline.

FIG. 3 shows mean plasma insulin profiles at baseline and week 4.

FIG. 4 shows changes in HbA_{1c} during the titration (PTO-MO) and maintenance (MO-M3) treatment periods.

FIG. 5 shows changes in fasting plasma glucose during the titration (PTO-MO) and maintenance (MO-M3) treatment periods.

DETAILED DESCRIPTION OF THE INVENTION

Healthy persons have a 24 hour basal secretion of insulin. In connection with meals there is an increased demand for insulin and via a complex feed-

back mechanism the pancreas is stimulated to fulfil the demand. After a while, the insulin level again decreases to the basal level.

For the first many years of the disease, dietary restrictions may help NIDDM patients to compensate for the earliest manifestation of their disease which is the decreasing ability of their pancreas to secrete the amount of insulin required in order to control the post prandial blood glucose. At a more progressed state of the disease, also the basal insulin secretion becomes insufficient. When medical treatment becomes necessary, an oral hypoglycemic agent will often be prescribed.

Most of the oral hypoglycemic agents presently in use have a fairly long biological half-life. This implies that when they are administered two or three times per day, which is usually the case, the insulin level will almost constantly be higher than corresponding to the basal level. On the other hand, the peak levels of insulin seen in healthy persons in connection with meals will not be achieved. Such a regimen has certain disadvantages. Thus, it is believed that the diabetic late complications arc closely related to a less than optimal glycaemic control caused by, for example, a fairly constantly increased insulin level. Another disadvantage with the long-acting hypoglycemic agents is that they to a very high degree dictate the life-style of the patient: once the patient has taken a long-acting hypoglycemic agent he has only little freedom to deviate from his dietary plan.

The regimen according to the present invention makes it possible for NIDDM patients to mimic the variations in the insulin level seen in healthy persons. Thus, if a patient has a satisfactory basal insu-

lin level, the extra insulin needed in connection with a meal can be secreted by a short stimulation of the pancreas in connection with the meal. Since a short-acting hypoglycemic agent is rapidly absorbed, it can be taken in connection with the meal, preferably shortly before or at the beginning of the meal, optionally during the meal or even shortly after. The resulting stimulation of the pancreas will produce a peak in the insulin level just when it is needed and due to the short half-life of the short-acting hypoglycemic agent, the insulin level will soon go down to the basal level again. The regimen according to the present invention makes it permissible for a NIDDM patient, to a certain degree, to act on an impulse as regards meals and thus adds to the patient's quality of life.

The designation "meal" as used in the present text is intended to mean breakfast, lunch dinner or midnight snack.

When the expression "meal-related" is used in the present text in connection with the administration of a short-acting hypoglycemic agent it preferably designates that the short-acting hypoglycemic agent is administered shortly before or at the beginning of the meal. However, the administration can obviously also take place during the meal or even shortly after without deviating from the idea behind the invention. Thus, the expression "meal-related" preferably means from about 10 minutes before the meal starts to about 10 minutes after the meal is finished, most preferred from about 5 minutes before the meal starts until the meal is finished, most preferred at the beginning of the meal.

If a NIDDM patient does not produce enough insulin to provide a satisfactory basal insulin level, the meal-related administration of a short-acting hypoglycemic agent can be supplemented with the administration of a long-acting hypoglycemic agent. Typically, a long-acting hypoglycemic agent will be administered once, twice or three times per day. Thus, in cases where there is a need to supplement the meal-related administration of a short-acting hypoglycemic agent with a long-acting one, the long-acting one can either be administered at separate hours or together with the short-acting one, optionally in the same tablet or capsule. The advantage of a combined administration is that it is likely to give an improved compliance with the prescribed regimen.

One advantage which can be expected from the regimen according to the present invention is that it, due to its simplicity, will improve the patients' compliance.

Another advantage is that no long-time planning of meals is needed: if the patient bas an extra meal he takes an extra tablet, if he skips a meal, he takes no tablet.

A further advantage which can be expected from this regimen is that the patients will have fewer serious diabetic late complications.

Repaglinide is a short-acting hypoglycemic agent with a short half-life. Examples of other short-acting hypoglycemic agents with a short half-lives are gliquidone and A-4166.

Examples of long-acting hypoglycemic agents are biguanides such as metformin and sulphonylureas such as chlorpropamide, tolbutamide, glibenclamide, glibornuride, gliclazide and glipizide. A further ex-

ample of a long-acting hypoglycaemic agent is troglitazone.

The particular hypoglycemic agent or agents to be used and the optimal dose level for any patient will depend on a variety of factors including the efficacy of the specific agent employed, the age, body weight, physical activity, and diet of the patient, on a possible combination with other drugs, and on the severity of the case. It is recommended that the dosage of the hypoglycemic agent or agents of this invention be determined for each individual patient by those skilled in the art.

When repaglinide is given—either alone or in combination with a biguanide or a sulphonylurea or another type of OHA—the amount of repaglinide is preferably in the range of from 0.01 mg to 6 mg, more preferred in the range from 0.2 mg to 5 mg per meal.

When metformin is given in combination with repaglinide, the daily dosage is preferably in the range of from 200 mg to 3000 mg per day.

The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, both separately and in any combination thereof, be material for realizing the invention in diverse forms thereof.

EXAMPLES

Example 1

Repaglinide can be Given in a Flexible Dosing Regimen to Patients with Type 2 Diabetes

As evidenced by the present, study, the short duration of action ($T_{½}$ = one hour) makes repaglinide suitable for a meal-related dosing regimen and provides a more flexible everyday life for people with diabetes.

In a single-centre, randomised, open-label, parallel group comparison study it was investigated whether repaglinide given preprandially will maintain glycaemic control in patients who skip a meal (lunch) or have an extra meal (bedtime snack) [mixed regimen] as compared with those who have three regular meals [fixed regimen].

A total of 25 diet-treated patients with type 2 diabetes were enrolled (18 men and 7 women) and given a fixed 1 mg dose of repaglinide preprandially (therapeutic dose range: 0.5-4 mg). After one week of stabilisation patients were randomised to the mixed or fixed regimen for a period of 21 days if blood glucose was >140 mg/dl.

Mean fructosamine values decreased ($p<0.05$) in both groups (fixed: 3.10 to 2.68 mmol/l; mixed: 3.37 to 2.85 mmol/l) with no significant difference between regimen groups. Mean fasting blood glucose (FBG) showed no statistically significant differences between the fixed and mixed groups. Mean FBG decreased to approximately 120 mg/dl in both groups and the difference was not statistically significant. Based on a 37-point blood glucose profile, AUC over 24 hours was not statistically significant between the fixed and mixed groups. When lunch was omitted, blood glucose levels remained stable until next meal. Both dose regimens were well tolerated and no hypoglycaemic episodes or serious adverse events were reported.

Thus, this study demonstrates that patients who occasionally deviate from the recommended meal plan may add an extra meal or skip one, taking repaglinide only when they have a meal, and still maintain their glycaemic control without adverse effect.

Example 2

Improved G1ycaemic Control with Repaglinide in NIDDM with 3 Times Daily Meal Related Dosing

Abstract

Repaglinide belongs to a new chemical class of insulin secretagogues and is a short-acting and rapid acting insulin releaser. The potential impact of tailoring insulin release to meal in-take was investigated in a study comparing 3 times daily dosing with repaglinide just before meals to the same dosage administered twice daily. Eighteen OHA-naive NIDDM patients entered a 4-week, single centre, double-blind study, and were randomised to either 0.25 mg repaglinide before breakfast, lunch and dinner (REP3), or 0.5 mg before breakfast, placebo at lunch, and 0.25 mg before dinner (REP2). After two weeks the doses were doubled. At baseline, blood glucose, insulin, and C-peptide profiles were identical between the two groups. After 4 weeks, fasting blood glucose had decreased significantly in both groups (REP2: 11.2 to 9.6 mmol/l and REP3: 11.2 to 8.4 mmol/l). The overall glycaemic control was better in REP3 when compared with REP2, as blood glucose ($AUC_{0\text{-}24\ h}$) was 8.91 mmol/l in REP2 and 7.00 mmol/l in REP3 ($P<0.05$). The same significant difference was also found with glucose AUC (0-16 h). This difference in improvement of glycaemic control was reflected in a significant decrease in HbA_{1c} levels in REP3, from 7.5 to 6.5% ($p<0.05$), while HbA_{1c} decreased non-

significantly in REP2 (from 7.1 to 6.8%). In both groups plasma insulin decreased to pre-treatment levels before the next meal and there was no increase in plasma insulin during the night time in comparison with pretreatment levels.

In summary, repaglinide treatment caused significant improvement in glycaemic control in OHA-naive NIDDM patients and administration of the same total daily repaglinide dose showed additional advantages in regard to glycaemic control when given before the three main meals as compared to 2 times daily. At the same time it was possible to avoid both between meals and nocturnal hyperinsulinemia.

Introduction

Repaglinide is a novel insulin secretagogue, which acts on the ATP-sensitive potassium channel in pancreatic ß-cells, but binds to a different site from sulphonylureas. Repaglinide has been developed for the treatment of patients with NIDDM whose blood glucose is not adequately controlled by diet alone. Because repaglinide is rapidly absorbed from the gastrointestinal tract and has a short plasma half-life, it is well suited for meal-related administration. The present study was designed to investigate the effects on glycaemic control of repaglinide when given at the same daily dose either morning and evening or preprandially at the three main meals.

Methods

This was a double-blind, placebo-controlled study involving patients with NIDDM, aged 40 to 70 years, with a body mass index >25 kg/m^2, fasting blood glucose (FBG) between 6.5 and 13 mmol/l, HbA_{1c} <11% and fasting C-peptide >0.3 pmol/ml. Of 18 patients enrolled, 17 were randomised to 4 weeks treatment

with either 0.25 mg repaglinide three times daily before the three main meals (REP3), or 0.5 mg repaglinide before breakfast, placebo before lunch and 0.25 mg before dinner (REP2). After 2 weeks, the doses were doubled to 0.5 mg before each meal (REP3) and 1 mg+0.5 mg (REP2). Each patient was seen at three visits during the 4-week study period. A 24-hour hormonal and metabolic profile was examined at baseline and day 28.

Results

Eight patients in the REP3 group and 9 patients in the REP2 group completed the study.

Glycemic Control

After 4 weeks of treatment, blood glucose had decreased in both the REP3 and REP2 groups ($P<0.01$) (FIG. 1). However, preprandial blood glucose values were 1 to 2 mmol/l lower with REP3 than with REP2, and postprandial values were significantly lower, by about 2.5 mmol/l ($P<0.05$).

Mean FBG (±SEM) decreased significantly in both groups ($P<0.001$). In the REP3 group, the decrease was from 11.1±1.24 mmol/l to 8.4±1.01 mmol/l, whilst in the REP2 group, the decrease was from 11.3±0.73 mmol/l to 9.6±0.7 mmol/l. HbA_{1c} (±SEM) also decreased in both groups after 4 weeks of treatment (REP3: 7.51±0.78% vs 6.51±0.64%; REP2: 7.12±0.24% vs 6.84±0.34%), but the decrease was only statistically significant in the REP3 group ($P=0.004$).

When $AUC_{0\text{-}24\ h}$ for glucose after 4 weeks of treatment was plotted versus $AUC_{0\text{-}24\ h}$ for glucose at baseline (FIG. 2), the slope estimates for the REP3 and REP2 groups differed significantly from one another ($P<0.04$). A similar trend towards greater glycaemic

control with REP3 than with REP2 was observed for $AUC_{0\text{-}16\ h}$, though the difference between the groups only just reached statistical significance.

Circulating Insulin and C-Peptide

There were no significant differences between the REP3 and REP2 groups in preprandial or postprandial plasma insulin or plasma C-peptide values during the study. Normed $AUC_{0\text{-}24\ h}$ for plasma C-peptide increased in both groups after 4 weeks of treatment. Normed $AUC_{0\text{-}24\ h}$ for plasma insulin increased by 20% in the REP2 group and 35-40% in the REP3 group (FIG. 3), but the difference was not significant. In both treatment groups, plasma insulin decreased to pre-treatment levels before the next meal, and there was no increase in plasma insulin during the night in comparison with pre-treatment levels.

Plasma Repaglinide

The pharmacokinetic profile of repaglinide was characterised by a high peak value in the morning in the REP2 group, and a high peak in the afternoon in the REP3 group. However, the mean $AUC_{0\text{-}9\ h}$ and $AUC_{0\text{-}24\ h}$ for repaglinide were similar in both groups, showing that both groups received matching total daily drug exposure.

Safety Results

No serious adverse events were reported in either treatment group. The only non-serious adverse events were mild hypoglycemic episodes and one case of influenza

Conclusions

Repaglinide produced a significant improvement in glycaemic control in NIDDM patients, with only mild adverse events at the dose levels used. While the two treatment regimens (twice daily and three times daily preprandially) had similar insulin secretion rates, and did not cause 24-hour hyperinsulinemia, the data indicate that greater metabolic control is achieved when repaglinide is dosed prior to the three major meals as compared to before just breakfast and dinner.

Example 3

Additional Treatment with Repaglinide Provides Significant Improvement in Glycemic Control in NIDDM Patients Poorly Controlled on Metformin

Abstract

This multi centre, randomised trial was designed to compare the effect on glycaemic control of repaglinide (REP) in combination with metformin (MET) against monotherapy with either drug in NIDDM patients inadequately controlled on MET alone (mean IIbA_{1c}: 8.5%). Eighty three patients were included in this three-armed, double-blind, double-dummy parallel group study. After a 4-5 week run-in period on their usual dose of MET, patients were randomized to either REP or MET monotherapy, or REP+MET combination therapy. The MET dose was kept constant throughout the study (1-3 g/day). The REP dose was determined during a 4-8 week titration phase (initial REP dose: 0.5 mg three times a day before meals; maximum dose: 4 mg three times a day before meals). A 3-month maintenance period followed the titration phase. From the baseline to final visit, combination therapy with MET+REP significantly ($P<0.005$) im-

proved glycemic control compared with REP or MET monotherapy (mean change in HbA_{1c}: -1.41% (MET+REP), -0.38% (REP), -0.33% (MET); mean change in fasting blood glucose (mmol/l): -2.18 (MET+REP), 0.49 (REP), -0.25 (MET). No statistical differences were seen between the two monotherapies and MET+REP combination therapy with respect to fasting insulin and C-peptide levels, and lipid profiles. MET and MET+REP treatment caused more gastrointestinal side effects than REP treatment. No severe hypoglycemic events were observed in any group. In conclusion, REP treatment provided the same glycemic control as MET with less gastrointestinal side effects. REP+MET therapy induced significant improvements in metabolic control in contrast to either REP or MET, bringing HbA_{1c} down into the range of acceptable control. The data also suggest that the combination of REP and MET may have synergistic properties in this type of patient.

Introduction

Repaglinide (REP) is a novel oral hypoglycemic agent which has been developed for the treatment of patients with NIDDM whose blood glucose is not controlled by dietary measures alone. The drug is rapidly absorbed, has a short plasma half-life, binds to a different site from sulfonylureas on the ATP-sensitive potassium channel on pancreatic ß-cells, and is excreted via the bile. Repaglinide (REP) stimulates an insulin release profile similar to the physiological postprandial state. As metformin (MET) and REP have complementary mechanisms of action, the aim of the present study was to investigate the efficacy and safety of REP as combination therapy with MET in patients inadequately treated with MET alone.

Methods

This study was a randomised, double-blind, parallel group trial performed at 9 centres in Australia. Eighty-three patients with NIDDM, aged 40-75 years, a body mass index of >21 kg/M^2, and inadequately controlled (HbA_{1c}>7.1%) after more than 6 months of MET treatment were enrolled. After a 4-5 week open baseline period of MET treatment, patients were randomised either to continue on MET at their usual dose (1-3 mg/day) or to treatment with a combination of MET and REP or REP alone. The dose of REP was determined during a 4-8 week titration period (initial dose 0.5 mg three times daily preprandially (three times a day before meals), maximum dose 4.0 mg three times a day before meals). The dose reached at the last titration step was continued during a 3-month maintenance period. The patients were seen at eight scheduled visits.

Results

A total of 83 patients were enrolled in the trial (MET+REP: 27; REP: 29; MET: 27), of whom 74 completed the study (MET+REP: 27; REP: 26; MET: 21).

Glycemic Control and Metabolic Indices

For patients in the MET+REP group, mean HbA_{1c} and fasting plasma glucose (FPG) decreased significantly from 8.32 to 6.91% (p P<0.005) and from 10.22 to 8.04 mmol/l (P<0.005), respectively between baseline and the final visit (FIGS. 4 and 5). There were no significant changes in either parameter for the MET and REP groups (Table 1).

Fasting insulin and C peptide levels increased significantly during the study in the MET+REP and

REP groups (P<0.05), but not in the MET group (Table 2).

Patients in the REP group had a small but statistically significant increase in total, HDL- and LDL-cholesterol levels during the study (P<0.05). HDL-cholesterol also increased in the MET group (P<0.05) (Table 3).

Safety Evaluation

A total of 339 adverse events were reported, of which 27 were considered probably or possibly related to study drug.

The frequency of drug-related adverse events was higher in the MET+REP group (59.3%) than in the monotherapy groups (REP: 25.0%; MET: 14.8%). MET+REP and MET treatment caused more gastrointestinal side effects than REP treatment (MET+REP: 14.8%; MET: 7.4%; REP: 3.6%). There were no statistically significant differences between the treatment groups in laboratory tests or vital signs.

Nine patients (33.3%) in the MET+REP group reported hypoglycemic episodes, compared to 3 (17.9%) in the REP group and none in the MET group. None of the hypoglycemic episodes were severe. One third of the patients with hypoglycemic episodes had these in the titration phase. One patient in the MET+REP group recorded 12 of the 30 episodes reported.

During the study, the mean body weight increased in the MET+REP group (+2.4±0.5 kg, P<0.005) and REP group (+2.98±0.49 kg, P<0.05), but decreased in the MET group (-0.86±0.51 kg, NS). The difference between the MET+REP and MET groups was statistically significant (P<0.05).

TABLE 1

Mean change in HbA_{1c} (%) and fasting plasma glucose (FPG) from baseline to the end of the 3-month maintenance period.

	Change in HbA_{1c} (%)	95% C.I.	Change in FPG (mmol/l)	95% C.I.
Metformin/ repaglinide	-1.41 ± 0.23	[-1.87; -0.95]*	-2.18 ± 0.45	[-3.07; -1.28]*
Repaglinide	-0.38 ± 0.23	[-0.84; 0.08]	0.49 ± 0.47	[-0.44; 1.42]
Metformin	-0.33 ± 0.24	[-0.80; 0.15]	-0.25 ± 0.47	[-1.18; 0.68]
Metformin/ repaglinide vs repaglinide	-1.03 ± 0.32	[-1.78; -0.29]*	-2.66 ± 0.65	[-4.14; -1.18]*
Metformin/ repaglinide vs metformin	-1.08 ± 0.33	[-1.84; -0.33]*	-1.92 ± 0.65	[-3.40; -0.44]*

Data are means ± SEM. *P< 0.05

TABLE 2

Mean change in fasting insulin and C peptide from baseline to the end of the maintenance treatment period.

Treatment groups	Change in fasting insulin (mU/t)	95% C.I.	Change in C peptide (mmol/l)	95% C.I.
Metformin/ repaglinide	4.23 ± 1.50	[1.24; 7.23]*	0.17 ± 0.07	[0.03; 0.30]*
Repaglinide	4.04 ± 1.56	[0.93; 7.16]*	0.18 ± 0.07	[0.03; 0.30]*
Metformin	1.05 ± 1.60	[-2.13; 4.23]	0.02 ± 0.07	[-0.13; 0.16]
Metformin/ repaglinide vs repaglinide	0.19 ± 2.17	[4.78; 5.15]	-0.01 ± 0.10	[-0.24; 0.21]
Metformin/ repaglinide vs metformin	3.18 ± 2.19	[-1.84; 8.20]	0.15 ± 0.10	[-0.07; 0.38]

Data are means ± SEM. *P< 0.05.

TABLE 3

Changes (mean ± SD) in lipid profiles (mmol/l) between baseline and the end of the maintenance treatment period.

	MET	MET+REP	REP
Total cholesterol	0.13 ± 0.13	0.13 ± 0.12	0.38 ± 0.12*
HDL cholesterol	0.07 ± 0.03*	0.05 ± 0.03	0.09 ± 0.03*
LDL cholesterol	0.10 ± 0.12	0.11 ± 0.11	0.41 ± 0.12
Triglycerides	-0.20 ± 0.17	-0.10 ± 0.16	0.09 ± 0.16

*$P < 0.05$

Conclusions

Combination therapy with REP and MET provides better glycemic control than either REP or MET monotherapy in NIDDM patients who are inadequately controlled on metformin alone. Indeed, MET+REP treatment reduced HbA_{1c} of this group of patients to the target value recommended by the American Diabetes Association (<7%).

What is claimed is:

1. A pharmaceutical composition comprising repaglinide and metformin together with a suitable carrier.

2. A pharmaceutical composition of claim 1 provided in the form of a tablet.

3. A pharmaceutical composition of claim 1 provided in the form of a capsule.

4. A method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin.

5. A kit for use in the treatment of a patient having non-insulin dependent diabetes mellitus (NIDDM), said kit comprising an amount of repaglinide formulated for administration to said patient and an amount of metformin formulated for administration to said patient.

* * * * * [In original]

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation or Composition) and/or Method of Use

NDA NUMBER
NDA 20-741

NAME OF APPLICANT / NDA HOLDER
Novo Nordisk Pharmaceuticals, Inc.
100 College Road West
Princeton, NJ 08540 USA

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME
Prandin

ACTIVE INGREDIENT(S)	STRENGTH(S)
Repaglinide	0.5 mg 1.0 mg 2.0 mg

DOSAGE FORM	APPROVAL DATE OF NDA OR SUPPLEMENT
Tablet, oral	12/22/1997

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) within thirty (30) days after approval of an NDA or supplement or within thirty (30) days of issuance of a patent as required by 21 CFR 314.53(c)(2)(i) at the address provided in 21 CFR 314.53(d)(4). To expedite review of this patent declaration form, you may submit an additional copy of this declaration form to the Center for Drug Evaluation and Research "Orange Book" staff.

For hand-written or typewriter versions of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.

4. Patent

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
US 6,677,358 B1	01/13/2004	06/12/2018

d. Name of Patent Owner	Address *(of Patent Owner)*	
Novo Nordisk A/S	Novo Allé	
	City/State 2880 Bagsvaerd	
	ZIP Code Denmark	FAX Number *(if available)*
	Telephone Number +45 444 48888	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

Highly Confidential A801 NOVO-1370130

For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement?	☑ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA?	☐ Yes	☑ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of the declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.)	☐ Yes	☑ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug substance if:

- the answers to 2.1 and 2.2 are "No," or,
- the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,
- the answer to 2.3 is "Yes" and there is no response to 2.4, or,
- the answer to 2.5 or 2.6 is "Yes."
- the answer to 2.7 is "No."

3.1 Does the patent claim the approved drug product as defined in 21 CFR 314.3?	☑ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug product if:

- the answer to question 3.1 is "No," or,
- the answer to question 3.2 is "Yes," or,
- the answer to question 3.3 is "No."

4. METHOD OF USE

Sponsors must submit the information in section 4 separately for each patent claim claiming an approved method of using the approved drug product. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more approved methods of using the approved drug product?		☑ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim an approved method of use of the approved drug product?	☑ Yes	☐ No
1			
4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the approved labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Use of Prandin tablets in combination with metformin to lower blood glucose in patients whose hyperglycemia cannot be controlled by sucrose, diet and either repaglinide or metformin alone.		

Highly Confidential

4.2b If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description.	Use: *(Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)* Use of repaglinide in combination with metformin to lower blood glucose.

FDA will not list the patent in the Orange Book as claiming the method of use if:

- the answer to question 4.1 or 4.2 is "No," or
- if the answer to 4.3 is "Yes" and the information requested in 4.2b and 4.2b is not provided in full.

For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

8.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

8.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	2/5/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(1).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Barry Reit, Ph.D.	
Address 100 College Road West	City/State Princeton, NJ
ZIP Code 08540	Telephone Number (609) 987-5822
FAX Number *(if available)* (609) 987-3916	E-Mail Address *(if available)* brei@novonordisk.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Highly Confidential NOVO-1370132

CARACO
PHARMACEUTICAL LABORATORIES, LTD.

ORIGINAL ABBREVIATED NEW DRUG APPLICATION

February 9, 2005.

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD-600
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

Re: ANDA Submission for Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg

Caraco Pharmaceutical Laboratories, Ltd. hereby submits this Original Abbreviated New Drug Application, which provides for Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg in accordance with Section 505 (j) of the Federal Food Drug and Cosmetic Act. The subject drug is a prescription drug formulated as an immediate release oral tablet.

Caraco Pharmaceutical Laboratories, Ltd. will manufacture the Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg, in a 100-count with a child-resistant cap, 500-count and 1000-count HDPE plastic bottle with a non child-resistant cap as the final drug product at its facility located at 1150 Elijah McCoy Drive, Detroit, Michigan 48202. Caraco has also packaged these tablets in a 30-count size with child-resistant caps, and will utilize the stability to qualify future smaller count sizes. Due to unsatisfactory stability results for the 30 count size (Repaglinide Tablets, USP, 0.5 mg, lot # 4760A); Caraco will not seek approval for the count sizes less than 100 count, until satisfactory stability

data is generated. The product will be launched with 100 count, 500 count and 1000 count bottles of tablets. The Drug Substance Repaglinide, USP utilized for the exhibit lot was manufactured by Sun Pharmaceutical Industries Ltd. Please refer to the Drug Master File (DMF) for a full description of the facility.

This ANDA also provides support for the addition of an alternate packaging location for this product. Although the exhibit lot was packaged at Caraco, it is our plan to also validate packaging at the alternate packaging site Future Pak, Ltd. (Registration # 1824909) located at 24700 Crest View Ct. Farmington Hills, MI-48335. A brief explanation of the packaging processes and related documents are contained in Section XIII, Packaging Material Controls, of this ANDA.

Please refer to the accompanying Table of Contents for a list of the data supporting this submission. These data have been presented in 14 volumes consistent with the Office of Generic Drugs Policy and Procedure Guide #30-91 entitled "Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application" dated April 10, 1991, and including the changes described in the Guidance for Industry entitled "Organization of an ANDA", and published by the Office of Generic Drugs dated February 1999.

The Reference Listed Drug (RLD) for this product is Prandin® tablets, by the innovator Novo Nordisk Pharmaceuticals, Inc. This Product shows no approved generics in the Orange Book Listing, Caraco is seeking an AB classification code, i.e. Product meeting necessary bioequivalence requirements. To demonstrate its bioequivalence to the listed drug, Caraco's proposed drug, **Repaglinide Tablets, USP, 0.5**

mg, 1 mg and 2 mg, has undergone, "A Randomized, Open Label, Two Treatment, Two Period, Two Sequence, Single Dose, Crossover, Bioequivalence Study of Repaglinide 2 mg Tablets of Caraco Pharmaceuticals Laboratories Ltd., USA, and PRANDIN® 2 mg Tablets of Novo Nordisk Pharmaceuticals, Inc. NJ, In Healthy Human Adult Subjects Under Fasting Conditions" (B004034), in 26 healthy volunteers to demonstrate its bioequivalence to the listed drug. The fasting study B004024, was repeated as study B004034 which exhibited a low Cmax.

Caraco's proposed drug, **Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg**, has also undergone A Randomized, Open Label, Two-Treatment, Two-Period, Two-Sequence, Single Dose, Crossover, Bioequivalence Study of Repaglinide 2 mg Tablets of Caraco Pharmaceuticals Laboratories Ltd., USA, and PRANDIN® 2 mg Tablets of Novo Nordisk Pharmaceuticals, Inc. USA, In Healthy Human Adult Subjects Under Fed Conditions" (B004025), in 25 healthy volunteers to demonstrate its bioequivalence to the listed drug.

The clinical portion of the fasting study B004034, was conducted by SPARC Bioresearch Pvt. Ltd. and the clinical portion of the *in vivo* Bioequivalence study under Fed (B004025) and Fasting (B004024 repeated by SPARC), were conducted by Lotus Labs Pvt. Ltd. The Bioanalytical Analysis for all studies was completed by SPARC Bioresearch Pvt. Ltd. Caraco Pharmaceuticals Laboratories, Ltd., is requesting a waiver from the requirements of submission of evidence demonstrating the in vivo bioequivalence of its Repaglinide Tablets, USP, 0.5 mg and 1 mg to the listed drug, Prandin® tablets. A request for Waiver is included in section VI subpart 4.

Caraco Pharmaceutical Laboratories, Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg, are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same standards of strength, quality, purity and identity as the listed drug, Prandin® tablets.

We are requesting twenty-four months expiration dating for this product based on the 3 month accelerated stability and 3 month controlled room temperature data enclosed herein in section XVI, Stability of Finished Dosage Form, subpart 4. At the FDA's request we will provide samples of the bulk drug substance and finished dosage form. This product is covered under a USP monograph and complies with the current compendia.

A copy of the Table of Contents has been provided in the front of each volume of the archival and review copies of this original abbreviated new drug application. The Archival copy consists of Volumes 1-14 and is bound in the blue binders. The Pharmacokinetics section is bound in the required orange binders and consists of 10 volumes. The Pharmacokinetics section includes sections I through VII of the archival copy (Volumes 1-10) containing the two bioequivalence studies. The Review copy contains the Chemistry, Manufacturing and Controls information, corresponding to Volumes 1, 11, 12, 13 and 14 of the Archival copy.

Caraco Pharmaceutical Laboratories, Ltd. is also submitting a complete and true copy of the CMC section from this application designated as the "field copy" to the FDA Detroit District Office (300 River Place, Suite 5900, Detroit, Michigan 48207). The Detroit District office has the inspection responsibilities

for the facility listed in this application, Caraco Pharmaceutical Laboratories, Ltd. The signed certification of this submission is located in section XXI subpart 4, in volume 20 of the archival copy.

In Compliance with 21 CFR 314 covering FDA pre-approval inspections of manufacturing sites, the Detroit District Office last inspected Caraco Pharmaceutical Laboratories from November 7 to December 2, 2002.

Caraco requests that FDA confirm whether, under the Hatch-Waxman Amendment to the Federal Food Drug and Cosmetic Act, our submission is the "first ANDA to file", containing a Paragraph IV Patent Certification to the innovator, Novo Nordisk Pharmaceuticals' product Prandin®. If you have any questions, please feel free to call me at (313) 556-4103.

Sincerely,

/s/ Susan Banks-Williams, Ph.D.
Susan Banks-Williams, Ph.D.
Director, Regulatory Affairs

Caraco Pharmaceutical Laboratories, Ltd.
ANDA for Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg

III. Certifications (continued)

1. Patent Certification (continued)

iv. Paragraph IV Certification for U.S. Patent No. 6,677,358 (continued)

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.94(a)(12)(i)(A)(4) and 21 CFR 314.95, Caraco Pharmaceutical Laboratories Ltd hereby states that, upon receipt from the FDA of an acknowledgment letter stating that this ANDA is sufficiently complete to permit a substantive review, it will give the notice required by Section 505(j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.95 to Novo Nordisk A/S, Bagsvaerd (DK), owner of U.S. Patent No. 6,677,358, and to Novo Nordisk Pharmaceuticals, Inc., 100 College Road West, Princeton, NJ 08540, the holder of the NDA for PRANDIN® (Repaglinide oral tablet).

This notice to Novo Nordisk, (Dk) and to Novo Nordisk Pharmaceuticals Inc, NJ, which will be sent by certified mail, return receipt requested, shall meet the requirements of 21 CFR 314.95(a) and 21 CFR 314.95(c).

Concurrently with sending the notice to Novo Nordisk, (Dk) and to NovoNordisk Pharmaceuticals Inc, NJ, Caraco Pharmaceutical Laboratories Ltd. will, as required by 21 CFR 314.95(b), amend

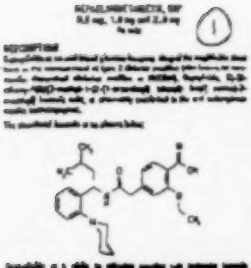
its ANDA for **Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg** to include a certification that the notice has been provided to each person identified under 21 CFR 314.95(a) and that the notice met the content requirements of 21 CFR 314.95(c).

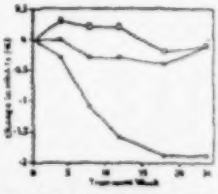
CARACO PHARMACEUTICAL LABS. LTD.

/s/ Robert Kurkiewicz
Robert Kurkiewicz
Senior Vice President, Technical
Caraco Pharmaceutical
Laboratories, Ltd.
1150 Elijah McCoy Drive
Detroit, MI 48202

2/9/05
Date

* * * *





DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Caraco Pharmaceutical Laboratories Ltd.	2/9/2005
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number** (Include Area Code)
(313) 871 8400	(313) 871 8314
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 1150 Elijah McCoy Drive, Detroit, MI 48202	**AUTHORIZED U.S. AGENT NAME & ADDRESS** (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)	PROPRIETARY NAME (trade name) IF ANY
Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any): See continuation sheet 1

CODE NAME (If any):

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	0.5 mg, 1 mg and 2 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Lowers the blood glucose in patients with type 2 diabetes mellitus (NIDDM)

APPLICATION DESCRIPTION

APPLICATION TYPE (check one)
☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE: ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug: Prandin® Holder of Approved Application: Novo Nordisk Pharmaceuticals, Inc.

TYPE OF SUBMISSION (check one): ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO APPENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY (MANUFACTURING AND CONTROLS) SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY: ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Original Abbreviated New Drug Application

PROPOSED MARKETING STATUS (check one): ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 14 THIS APPLICATION IS: ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC
electronic labeling

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary), include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See continuation sheet 1
This site is ready for inspection

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, DMFs, and DMFs referenced in the current application)
See continuation sheet 2

FORM FDA 356h (4/03) PAGE 1 OF 1

1

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ATTORNEYS EYES ONLY

This application contains the following items: *(Check all that apply)*	
☒	1. Index
☒	2. Labeling *(check one)* ☐ Draft Labeling ☒ Final Printed Labeling
☒	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☒	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☒	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☒	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☒	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☒	15. Establishment description (21 CFR Part 600, if applicable)
☒	16. Debarment certification (FD&C Act 306 (k)(1))
☒	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Susan M-Williams PhD	Susan Banks-Williams, Ph.D. Director, Regulatory Affairs	2/9/2005

ADDRESS (Street, City, State, and ZIP Code)	Telephone Number
1150 Elijah McCoy Drive, Detroit, MI 48202	(313) 871-8400

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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ATTORNEYS EYES ONLY

C0000016

Continuation Sheet 1 for FDA Form 356h

ANDA for Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg

Chemical/Biochemical/Blood Product Name (*if any*)

The chemical name is S(+)2-ethoxy-4(2((3-methyl-1-(2-(1-piperidinyl) phenyl)-butyl) amino)-2-oxoethyl) benzoic acid

Establishment Information

1. Drug substance

Repaglinide, USP:

Sun Pharmaceutical Industries Ltd. Acme Plaza, Andheri-Kurla Road Andheri (East), Mumbai - 400 059 India	Drug substance manufacturer

Contact: Mr. Ram Jhangiani
Phone: +91-22-8230102,
+91-22-8212128,
+91-22-8212115
Fax: +91-22-8212010

2. Drug Product Manufacturer

Caraco Pharmaceutical Laboratories, Ltd. 1150 Elijah McCoy Drive Detroit, MI 48202	A] Drug Product Manufacturer B] Finished Product and Stability Testing Site C] Packaging Site

Contact: Robert Kurkiewicz
Senior Vice President, Technical
Phone: 313-871-8400

Fax: 313-871-8314

Registration # 1833173

2. Drug Product Manufacturer (continued)

Future Pak Ltd.
24700 Crestview Ct.
Farmington Hills, MI
48335

C] Alternate Packaging Site

Contact: Steven J. Mead
President
Phone: 248-474-5511
Fax: 248-474-1524

Registration # 1824909

Continuation Sheet 2 for FDA Form 356h

ANDA for Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg

Cross References

DMFs referenced in the current application are as follows:

DMF#	Company
17825	Sun Pharmaceutical Industries Ltd.
5798	Quality Container Co.
100	BASF Chemical Company
3413	EMD Chemicals Inc.
8394	Ampacet Corporation
1016	Cheveron Phillips Chemical Company, LP
5828	Van Blarcom Closures, Inc.
16574	Mold Rite Plastics Inc.
6630	Ferro Corporation
8712	Epsilon Products Company
3782	Unipac Corporation
3720	Solvay Polymers

5036	Sunoco Chemicals (Formerly Equistar)
1584	Sunoco Chemicals
4075	Equistar Chemicals, LP
10562	Phillips Sumika Polypropylene Company
4544	Selig Sealing Products, Inc.
3644	Future Pak Ltd (Alternate Packaging Site)

II. Basis for Abbreviated New Drug Application Submission (§ 314.94 (a) (3))

Name of New Drug(s): **Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg**

Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Drive
Detroit, Michigan 48202

Name of Listed Drug(s): **PRANDIN® (repaglinide) NDA# 020741**

Mfd.By:
Novo Nordisk Pharmaceuticals, Inc.
100 College Road, West
Princeton, NJ 08540

III. Certifications

1. Patent Certification (§ 314.94 (a) (12))

Pursuant to 21 U.S.C. 355(j)(2)(A)(vii), Caraco Pharmaceutical Laboratories, Ltd's statement of Certification for all patents which claim the listed drug, PRANDIN® (repaglinide) tablets, referred to in this application or which claim a use of the listed drug have been provided in this section.

Patent Certification [Section 505(j)(2)(A)(vii) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.94(a)(12)]

Enclosed in this section is the statement of patent certification for Caraco's ANDA for **Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg.**

These statements are in accordance with the Food, Drug and Cosmetic Act, as amended December 8, 2003 (Prescription Drug and Medicare Improvement Act of 2003) and with the Code of Federal Regulations as amended and effective March 10, 2004.

III. Certifications (continued)

1. Patent Certification (continued)

i. Paragraph III Certification for U.S. Patent No. 5,312,924

In accordance with the Federal Food, Drug, and Cosmetic Act, as amended December 8, 2003, Patent Certification is hereby provided for our Abbreviated New Drug Application for Caraco's ANDA for **Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2mg.**

Caraco Pharmaceuticals Laboratories Ltd. hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 5,312,924, will expire on **September 05, 2006**, which is the expiration date listed in the Orange Book for this patent.

Caraco Pharmaceuticals Laboratories Ltd. will not market the drug product until the U.S. Patent No. 5,312,924 has expired.

CARACO PHARMACEUTICAL LABS. LTD.

/s/Robert Kurkiewicz — 2/9/05
Robert Kurkiewicz — Date
Senior Vice President,
Technical
Caraco Pharmaceutical
Laboratories, Ltd.
1150 Elijah McCoy Drive

III. Certifications (continued)

1. Patent Certification (continued)

ii. Paragraph III Certification for U.S. Patent No. 6,143,769

In accordance with the Federal Food, Drug, and Cosmetic Act, as amended December 8, 2003, Patent Certification is hereby provided for our Abbreviated New Drug Application for Caraco's ANDA for **Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg**.

Caraco Pharmaceuticals Laboratories Ltd. hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 6,143, 769 will expire on **September 05, 2006**, which is the expiration date listed in the Orange Book for this patent.

Caraco Pharmaceuticals Laboratories Ltd. will not market the drug product until the U.S. Patent No. 6,143, 769 has expired.

CARACO PHARMACEUTICAL LABS. LTD.

/s/ Robert Kurkiewicz — 2/9/05
Robert Kurkiewicz — Date
Senior Vice President,
Technical
Caraco Pharmaceutical
Laboratories, Ltd.
1150 Elijah McCoy Drive

III. Certifications (continued)

1. Patent Certification (continued)

iii. Paragraph III Certification for U.S. Patent No. RE37035

In accordance with the Federal Food, Drug, and Cosmetic Act, as amended December 8, 2003, Patent Certification is hereby provided for our Abbreviated New Drug Application for Caraco's ANDA for **Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg**.

Caraco Pharmaceuticals Laboratories Ltd. hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. RE37035 will expire on **March 14, 2009**, which is the expiration date listed in the Orange Book for this patent.

Caraco Pharmaceuticals Laboratories Ltd. will not market the drug product until the U.S. Patent No. RE37035 has expired.

CARACO PHARMACEUTICAL LABS. LTD.

/s/ Robert Kurkiewicz — 2/9/05
Robert Kurkiewicz — Date
Senior Vice President,
Technical
Caraco Pharmaceutical
Laboratories, Ltd.
1150 Elijah McCoy Drive

III. Certifications (continued)

1. Patent Certification (continued)

iv. Paragraph IV Certification for U.S. Patent No. 6,677,358

In accordance with the Federal Food, Drug, and Cosmetic Act, as amended December 8, 2003, Patent Certification is hereby provided for our Abbreviated New Drug Application for Caraco's ANDA for **Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg**.

Caraco Pharmaceuticals Laboratories Ltd. hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 6,677,358, which as per the expiration date listed in the Orange Book for this patent will expire on June 12, 2018, ***is invalid or will not be*** infringed by the manufacture, use or sale of Caraco's **Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg** for which this application is submitted.

CARACO PHARMACEUTICAL LABS. LTD.

/s/ Robert Kurkiewicz — 2/9/05
Robert Kurkiewicz — Date
Senior Vice President,
Technical
Caraco Pharmaceutical
Laboratories, Ltd.
1150 Elijah McCoy Drive

III. Certifications (continued)

1. Patent Certification (continued)

iv. Paragraph IV Certification for U.S. Patent No. 6,677,358 (continued)

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.94(a)(12)(i)(A)(4) and 21 CFR 314.95, Caraco Pharmaceutical Laboratories, Ltd. hereby states that, upon receipt from the FDA of an acknowledgment letter stating that this ANDA is sufficiently complete to permit a substantive review, it will give the notice required by Section 505(j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.95 to Novo Nordisk A/S, Bagsvaerd (DK), owner of U.S. Patent No. 6,677,358, and to Novo Nordisk Pharmaceuticals, Inc., 100 College Road West, Princeton, NJ 08540, the holder of the NDA for PRANDIN® (Repaglinide oral tablet).

This notice to Novo Nordisk, (Dk) and to Novo Nordisk Pharmaceuticals Inc., NJ, which will be sent by certified mail, return receipt requested,

shall meet the requirements of 21 CFR 314.95(a) and 21 CFR 314.95(c).

Concurrently with sending the notice to Novo Nordisk, (Dk) and to NovoNordisk Pharmaceuticals Inc., NJ, Caraco Pharmaceutical Laboratories Ltd. will, as required by 21 CFR 314.95(b), amend its ANDA for **Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg** to include a certification that the notice has been provided to each person identified under 21 CFR 314.95(a) and that the notice met the content requirements of 21 CFR 314.95(c).

CARACO PHARMACEUTICAL LABS. LTD.

/s/ Robert Kurkiewicz — 2/9/05
Robert Kurkiewicz — Date
Senior Vice President,
Technical
Caraco Pharmaceutical
Laboratories, Ltd.
1150 Elijah McCoy Drive

III. Certifications (continued)

2. Statement of Exclusivity (§ 314.94(a) (3))

Pursuant to 21 CFR § 314.94(a)(3)(ii), Caraco Pharmaceutical Laboratories, Ltd. hereby certifies that according to the information published in the list, the reference listed drug (PRANDIN® tablets) referred to in this application is entitled for marketing exclusivity under section 505(j)(4)(D) and 505(c)(3)(D)(ii) of the Federal Food, Drug, and Cosmetic Act. Details of marketing exclusivity are given below:

Exclusivity Code	Exclusivity expiration
I-367	October 21, 2005

Caraco Pharmaceuticals Laboratories, Ltd. intends to commercially market the Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg after FDA approval of its application and the expiration of exclusivity period.

/s/ Robert Kurkiewicz
Robert Kurkiewicz
Senior Vice President,
Technical
Caraco Pharmaceutical
Laboratories, Ltd.
1150 Elijah McCoy Drive

2/9/05
Date

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 77-571

Caraco Pharmaceutical Laboratories Ltd.
Attention: Susan Banks-Williams, Ph.D.
1150 Elijah McCoy Drive
Detroit, MI 48202

APR 07 2005

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Repaglinide Tablets USP, 0.5 mg, 1 mg and 2 mg

DATE OF APPLICATION: February 9, 2005

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 10, 2005

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice.

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/ RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/ SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

You must submit a copy of a court order or judgment, or a settlement agreement, or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (301)827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Peter Chen
Project Manager
(301) 827-5848

Sincerely yours,

/s/ [illegible]
Wm. Peter Richman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

PROSKAUER ROSE LLP

* * * *

[Address Omitted]

Charles Guttman
Member of the Firm
Direct Dial 212.969.3180
cguttman@proskauer.com

April 26, 2005

VIA REGISTERED MAIL

RETURN RECEIPT REQUESTED

Novo Nordisk A/S
Novo Allé
DK-2880, Bagsvaerd
Denmark

Novo Nordisk, Inc
100 College Road West,
Princeton, NJ 08540

Attn: Legal Counsel

Re: Notice of Certification Under 21 U.S.C. § 355(j)(2)(B)(ii) (§ 505(j)(2)(B)(ii) of Federal Food, Drug and Cosmetic Act) and 21 C.F.R. § 314.95

I. Caraco Pharmaceutical Laboratories Limited ("Caraco") of Detroit, Michigan, hereby certifies under 21 U.S.C. § 355(j) (2) (B) (ii) and 21 C.F.R. § 314.95(c)(1), to the following persons that it has filed an Abbreviated New Drug Application ("ANDA") for permission to sell Repaglinide Tablets, 0.5 mg, 1 mg, and 2 mg (Repaglinide Tablets) which is bioequivalent to Prandin®, Repaglinide Tablets, 0.5 mg, lmg, and 2 mg (Prandin).

1. Holder of New Drug Application (NDA 020741) for Prandin:

Novo Nordisk, Inc
100 College Road West,
Princeton, NJ 08540

2. Owner US Patent. No. 6,677,358 (the '358 Patent) listed in the Orange Book:

Novo Nordisk A/S
Novo A11é
DK.-2880, Bagsvaerd
Denmark

II. Pursuant to 21 U.S.C. § 355(j)(2)(B)(ii) and 21 C.F.R. § 314.95(c)(1), the United States Food and Drug Administration has received an ANDA from Caraco containing any required bioavailability and/or bioequivalence data showing that Caraco's proposed product is bioequivalent to Prandin (Repaglinide Oral Tablet) that is the subject of NDA 020741. The ANDA was submitted under 21 U.S.C. § 355(j)(1) and 2(A) with a paragraph IV certification to obtain approval to engage in the commercial manufacture, use, or sale of oral repaglinide oral tablets before the expiration of the '358 Patent which is listed in *Approved Drug Products with Therapeutic Equivalence Evaluation* ("Orange Book").

III. Pursuant to 21 C.F.R. § 314.95(c)(2), the ANDA filed by Caraco has been assigned ANDA No. 77-571 by the FDA.

IV. Pursuant to 21 C.F.R. § 314.95(c)(3), the established name for the proposed drug product is REPAGLINIDE; TABLET; ORAL.

V. Pursuant to 21 C.F.R. § 314.95(c)(4), the active ingredient for the proposed drug product is repagli-

nide. The strength and dosage forms of the proposed drug product are equivalent to 0.5 mg, 1 mg and 2 mg of repaglinide, in an oral, tablet form.

VI. Pursuant 21 C.F.R. § 314.95(c)(5), the following patent has been listed in the Orange Book and is alleged to be not infringed, unenforceable, and/or invalid:

US Patent No. 6,677,358 (expires June 12, 2018).

VII. Caraco alleges, and has certified to the FDA, that in its opinion and to the best of its knowledge, the patent listed above is invalid, unenforceable, and/or not infringed by the commercial manufacture, use, or sale of the drug product described by Caraco's ANDA. Pursuant to 21 U.S.C. § 355(j)(2)(b)(ii) and 21 C.F.R. § 314.95(c)(6), Caraco's detailed statement of the legal and factual basis for the certification set forth in Caraco's ANDA is contained in the attached Appendix.

VIII. Pursuant to 21 § 114.95(c)(7), the undersigned is authorized to accept service of process on behalf of Caraco at the address indicated below:

Charles Guttman
Proskauer Rose LLP
1585 Broadway
New York, New York 10036

IX. Pursuant to 21 U.S.C. § 355(j)(5)(C), this notice letter includes an Offer of Confidential Access to Application. As required by § 355(j)(5)(C)(i)(III), Caraco offers to provide confidential access to certain information from its ANDA No. 77-571 for the sole and exclusive purpose of determining whether an infringement action referred to in § 355(j)(5)(B)(iii) should be brought.

Section 355(j)(5)(C)(i)(III) allows Caraco to impose restrictions "as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information." That provision also grants Caraco the right to redact its ANDA to remove any information of no relevance to any issue of patent infringement in response to a request for Confidential Access under this offer.

As permitted by statute, Caraco imposes the following terms and restrictions on its Offer of Confidential Access:

(1) Caraco will permit confidential access to certain information from its proprietary ANDA No. 77-571 to attorneys from one outside law firm representing the Innovator; provided, however, that such attorneys do not engage, formally or informally, in patent prosecution for the Innovator. Such information (hereinafter, "Confidential Caraco information") shall be marked with the legend "CONFIDENTIAL".

(2) The attorneys from the outside law firm representing the innovator shall not disclose any Confidential Caraco Information to any other person or entity, including the Innovator employees, outside scientific consultants, and/or other outside counsel retained by the Innovator, without the prior written consent of Caraco's outside litigation counsel, Proskauer Rose LLP.

(3) As provided by § 355(j)(5)(C)(i)(III) the Innovator's outside law firm shall make use of the Confidential Caraco Information for the sole and exclusive purpose of determining whether an action referenced to in §355(j)(5)(B)(iii) can be brought and for

no other purpose. By way of example only, the Confidential Caraco information cannot be used to prepare or prosecute future or pending patent application by the Innovator, or in connection with any filing to or communication with the FDA relating to Caraco's ANDA No. 77-571. The Innovator's outside law firm agrees to take all measures necessary to prevent unauthorized disclosure or use of the Confidential Caraco Information, and that all Confidential Caraco Information shall be kept confidential and not disclosed in any manner inconsistent with this Offer of Confidential Access.

(4) The Confidential Caraco Information disclosed is, and remains, the property of Caraco. By providing the Confidential Caraco Information, Caraco does not grant the Innovator and/or the Innovator's law firm any interest in or license for, the Confidential Caraco Information.

(5) The Innovator's law firm shall, within thirty-five (35) days from the date that it first receives the Confidential Caraco Information, return to Caraco's outside litigation counsel, Proskauer Rose LLP, all Confidential Caraco Information and any copies thereof. The Innovator's law firm shall return to Proskauer Rose LLP all Confidential Caraco Information before any infringement suit is filed by Novo Nordisk, if suit is commenced before this 35-day period expires. In the event that the Innovator opts to file suit, none of the information contained in or obtained from any Confidential Caraco Information that Caraco provides will be included in any publicly-available complaint or other pleading.

(6) Nothing in this Offer of Confidential Access shall be construed as an admission by Caraco regarding

the validity, unenforceability and/or infringement of any U.S. Patent. Further, nothing herein shall be construed as an agreement or admission by Caraco with respect to the competency, relevance, or materiality of any such Confidential Caraco Information, document, or thing. The fact that Caraco provides Confidential Caraco Information upon request of the Innovator shall not be construed as an admission by Caraco that such Confidential Caraco Information is relevant to the disposition of any issue relating to any alleged infringement of the '358 patent, or to the validity of that patent.

(7) The attorneys from the Innovator's outside law firm will acknowledge in writing their receipt of a copy of these terms and restrictions prior to production of any Confidential Caraco Information. Such written acknowledgement shall be provided to Caraco's outside litigation counsel, Proskauer Rose LLP.

(8) This Offer of Confidential Access shall be governed by the laws of the State of New York.

Section 355(j)(5)(C)(i)(III) provides that any request for access that the Innovator makes under this Offer of Confidential Access "shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in [this] offer of confidential access" and that the "restrictions and other terms of [this] offer of confidential access shall be considered terms of an enforceable contract." Thus, to the extent that the Innovator requests access to Confidential Caraco Information, it necessarily accepts the terms and restrictions outlined above. Written notice requesting access under this Offer of Confidential Access should be made to:

Charles Guttman
Proskauer Rose LLP
1585 Broadway
New York, New York 10036
Tel: 212.969.3180
Fax: 212.969.2900

By providing this Offer of Confidential Access to Application, Caraco maintains the right and ability to bring a Declaratory Judgment action under 28 U.S.C. §§ 2201 *et seq.*, pursuant to 21 U.S.C.§ 355(j)(5)(C).

It is hereby certified that a copy of this Notice, together with the Appendix, has been sent by Registered Mail, Return Receipt Requested, to Legal Counsel of:

Novo Nordisk A/S
Novo Allé
DK-2880, Bagsvaerd
Denmark

Novo Nordisk, Inc
100 College Road West,
Princeton, NJ 08540

Very truly yours,

/s/ Charles Guttman
Charles Guttman
Proskauer Rose LLP
1585 Broadway
New York, New York 10036

APPENDIX OF DETAILED REASONS

The following constitutes Caraco's detailed statement of the factual and legal bases for Caraco's belief that US 6,677,358 (hereinafter, US '358) is not infringed by the commercial manufacture, use or sale of the drug product described in Caraco's ANDA. This detailed statement will not preclude Caraco from advancing any other grounds for invalidity, non-infringement, and/or unenforceability, or any other claim construction, of the '358 Patent in the event of litigation.

A. Innovator's Repaglinide Tablets and Label

Innovator's Prandin tablet contains repaglinide as the active ingredient in 0.5 mg, 1 mg and 2 mg strengths. The indications and usage in innovator's label includes indication as an adjunct to diet and exercise to lower the blood glucose in patients with type 2 diabetes mellitus and an indication for combination therapy use (with metformin or thiazolidinediones) to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise plus monotherapy with either agents.

B. Caraco's ANDA Drug Product and Label

The proposed drug product that is the subject of Caraco's ANDA No. 77-571 ("the ANDA drug product") is Repaglinide Tablets containing as the active ingredient repaglinide 0.5 mg, 1 mg and 2 mg. Caraco's proposed label does not include any indication for combination therapy with metformin.

C. The US '358 Patent and its Prosecution History

US '358, entitled "NIDDM Regimen," was issued

to Novo Nordisk on January 13, 2004. US '358 is based upon U.S. App. No. 09/459,526, filed December 13, 1999, which is a continuation of PCT App. No. PCT/DK98/00248, filed June 12, 1998, which is based upon U.S. Prov. App. No. 60/063,368, filed in the PTO on October 29, 1997. US '358 also claims the benefit of priority of an application filed in Denmark on June 13, 1997. Assuming all maintenance fees are paid, US '358 is expected to expire on June 12, 2018, as listed in the Orange Book.

US '358 describes a combination therapy for the treatment of NIDDM (Non-Insulin Dependent Diabetes Mellitus). US '358 contains 5 claims, of which claims 1, 4, and 5 are independent. Claim 1 claims a pharmaceutical composition comprising repaglinide and metformin together with a suitable carrier. Claim 4 claims a method for treating NIDDM comprising administering to a patient repaglinide in combination with metformin. Claim 5 claims a kit for use in treatment of a patient having NIDDM, the kit comprising an amount of repaglinide and an amount of metformin.

As originally filed, not all of the claims in App. No. 09/459,526 were restricted to the combination of repaglinide and merformin. Rather, some of the original claims merely recited the administration of a effective amount of a short-acting hypoglycemic agent, while other claims recited the combination of a short-acting hypoglycemic agent and a long-acting hypoglycemic agent. However, during the course of prosecution, Novo restricted all claims in App. No. 09/459,526 to the specific combination of repaglinide and metformin in order to distinguish over the prior art. Additionally, Novo emphasized that the prior art cited by the Examiner did not disclose the specific

combination of repaglinide and metformin for the treatment of NIDDM, and that this combination produces a "synergistic effect."

Based on the restriction of all claims to the combination of repaglinide and metformin and the arguments made by Novo including the submission of a Declaration Under 37 C.F.R. §1.132 of Dr. Sturis, the Examiner allowed the claims of US '358. In issuing a Notice of Allowance, the Examiner stated as Reasons for Allowance that "the present application is solely directed to the combination of repaglinide and metformin for use in treating, non-insulin dependent diabetes mellitus, and that "the combined administration of repaglinide and metformin resulted in an unexpected synergistic effect on blood glucose levels," citing the Declaration of Dr. Sturis.

Accordingly, US '358 was issued on January 13, 2004, with its present set of claims all of which are restricted to the combination of repaglinide and metformin.

D. Comparison of Caraco's Repaglinide Tablets and Labeling with the Claims of US '358

The Court of Appeals for the Federal Circuit ("Federal Circuit") has repeatedly stated that dirct infringement requires a two-step analysis. First, the claims of the patient in issue must be properly construed to determine their scope. Second, the accused device, product, or process must be compared to the properly construed claims. E.g., *Mars, Inc.* v. *H.J. Heinz Co.*, 377 F.3d 1369 (Fed. Cir. 2004); *Becton Dickinson & Co.* v. *C.R. Bard, Inc.*, 922 F.2d 792 (Fed. Cir. 1990). Infringement is found if the accused device, product, or process contains each and every element, either literally or by a substantial equiva-

lent, of at least one claim in the patent. E.g., *Charles Greiner & Co.* v. *Mari-Med Mfg, Inc.*, 962 F.2d 1031 (Fed. Cir. 1992). Furthermore, it is not possible to infringe a dependent claim without infringing the independent claim from which it depends. *Wahpeton Canvas Co.* v. *Frontier, Inc.*, 870 F.2d 1546 (Fed. Cir. 1989).

As recounted above, each of the independent claims in US '358 recites the specific combination of repaglinide and metformin. This includes claim 4 which claims a method for treating NIDDM comprising administering to a patient repaglinide in combination with metformin. The prosecution history described above demonstrates that the claims in US '358 were allowed only because they are restricted to this specific combination and Novo argued that this specific combination produces a synergistic effect.

Accordingly, by ascribing to the terms used in the independent claims of US '358 their plain and ordinary meanings as understood by a person of ordinary skill in the art, since such meanings do not create any ambiguities and since the specification and/or prosecution history do not clearly indicate that any different meanings are intended, the independent claims of US '358 must be construed as being restricted to the combination of repaglinide and metformin. Furthermore, the Doctrine of Prosecution History Estoppel precludes Novo from expanding the coverage of the claims to encompass anything which does not include this particular combination.

ANDA No. 77-571 of Caraco seeks approval to market Repaglinide Tablets alone and not in combination with metformin. Therefore, Caraco's product will not infringe claim 1 (directed to a pharmaceutical

composition) and claim 5 (directed to a kit used in the treatment of a patient having NIDDM) of US '358.

With regard to claim 4 (directed to a method for treating NIDDM), Caraco's ANDA does not seek approval to market repaglinide in combination with metformin, and Caraco's proposed label does not contain any indication or reference to the treatment of NIDDM by administering repaglinide in combination with metformin. Specifically, there is no listing under "Indications and Usage" or under "Dosage and Administration" in Caraco's proposed label for the combination of repaglinide and metformin.

Accordingly, Caraco's filing of ANDA No. 77-571 will not directly infringe claim 4 of US '358 under 35 U.S.C. 271(e)(2)(A). See, *Warner Lambert Co.* v. *Apotex*, 316 F.3d 1348 (Fed. Cir. 2003).

With regard to active inducement of infringement of claim 4, the Federal Circuit in *Warner-Lambert* also noted that "mere knowledge alone of possible infringement by others is insufficient to prove inducement." Rather, "specific intent and action to induce infringement must be proven." In the absence of any evidence that the ANDA applicant has or will promote or encourage doctors to infringe a method of treatment patent, active inducement of infringement is not proven.

Thus, in *Warner-Lambert*, the Federal Circuit concluded that the mere filing of an ANDA does not constitute direct infringement or active inducement of infringement of a method-of-use patent where the ANDA does not seek approval to market for the claimed use. As the Federal Circuit said:

> "The ANDA must be judged on its face for what an accused infringer seeks the FDA's approval

> to do. Section 271(e)(2) does not encompass 'speculative' claims of infringement. The statute explicitly defines the act of infringement as the filing of the ANDA. The infringement case is therefore limited to an analysis of whether what the generic drug maker is requesting authorization for in the ANDA would be an act of infringement if performed."

The decision rendered in the *Warner-Lambert* case is binding and controlling law. Therefore, Caraco's filing of ANDA No. 77-571 which seeks approval to market Repaglinide Tablets but which does not seek approval to market repaglinide in combination with metformin for treatment of NIDDM, and which does not contain an indication in the proposed label for combination therapy with metformin, will not directly infringe and will not constitute an act of actively inducing infringement of claim 4 of US '358.

For the reasons given above, Caraco's Repaglinide Tablets and its ANDA for marketing of Repaglinide Tablets will not infringe any of the claims of US '358.

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants.

Civil Action No.: 4:05 CV 40188
Judge Paul Gadola
Magistrate Judge Donald A. Scheer

FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs, Novo Nordisk A/S and Novo Nordisk Inc. (collectively "Novo Nordisk"), by their attorneys, allege:

1. This is an action for infringement of patents under the Patent Act of 1952, Title 35, United States Code, § 271 *et seq.* This Court has jurisdiction pursuant to Title 28, United States Code, §§ 1331 and 1338, Title 35, United States Code, § 271(e)(2), Title 28, United States Code §§ 2201 and 2202, and Title 21 United States Code § 355(j)(5)(c)(i). Venue in this District is proper under Title 28, United States Code, §§ 1391(b) and (c) and 1400(b).

2. Novo Nordisk A/S is a Danish corporation having a place of business at Novo Allé, DK-2880 Bagsvaerd, Denmark.

3. Novo Nordisk Inc. is a Delaware corporation having a place of business at 100 College Road West, Princeton, New Jersey.

4. Upon information and belief, Defendant Caraco Pharmaceutical Laboratories, Ltd. ("Caraco") is a Michigan corporation, having its principal place of business at 1150 Elija McCoy Drive, Detroit, Michigan; is doing business in this judicial district; and is subject to the jurisdiction of this Court pursuant to the laws of this State and Fed. R. Civ. P. 4.

5. Upon information and belief, Defendant Sun Pharmaceutical Industries, Ltd. ("Sun") is a corporation organized under the laws of India, having a place of business at Andheri Kurla Road, Andheri (East), Mumbai 400 059, India.

6. Upon information and belief, Sun has submitted to the jurisdiction of this Court by answering a portion of Novo Nordisk's original complaint.

7. Upon information and belief, Sun is doing business in this judicial district and is subject to the jurisdiction of this Court pursuant to the laws of this State and Fed. R. Civ. P. 4.

8. Upon information and belief, Sun is the parent company of Caraco and has controlled, participated in and/or directed the acts alleged in this complaint. Sun and Caraco are collectively referred to herein as "Defendants."

9. Novo Nordisk A/S is the owner by assignment of United States Patent No. 6,677,358 ("the '358 patent"), entitled "NIDDM REGIMEN", which issued on January 13, 2004. A copy of the '358 patent is attached as Exhibit A. "NIDDM" is and abbreviation for Non-insulin Dependent Diabetes Mellitus.

10. The '358 patent claims a pharmaceutical composition which includes repaglinide, metformin, and a carrier (claim 1) in the form of a tablet (claim 2) or a capsule (claim 3); a method for treating NlDDM by administering to a patient in need of treatment, repaglinide in combination with metformin (claim 4); and a kit which includes repaglinide and metformin (claim 5).

11. Novo Nordisk presently markets repaglinide under the registered trademark PRANDIN®.

12. PRANDIN® was approved on December 22, 1997, by the U.S. Food and Drug Administration ("FDA") for combination therapy of NIDDM with metformin. Novo Nordisk Inc. is the holder of this approval.

13. The listing for PRANDIN® in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (a.k.a. the "Orange Book") includes Novo Nordisk A/S's '358 patent.

14. Upon information and belief, Caraco filed an Abbreviated New Drug Application ("the ANDA") with the FDA. The ANDA is directed to repaglinide and its use and included a certification under Title 21, § 355(j)(2)(A)(vii)(IV) ("a paragraph IV certification") regarding Novo Nordisk A/S's '358 patent.

15. Upon information and belief, Sun directed, controlled and/or participated in the filing of the ANDA and stands to benefit directly should the ANDA be granted.

16. Caraco sent Novo Nordisk a "Notice of Certification under 21 U.S.C. § 355(j)(2)(B)(ii) (§ 505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act) and 21 C.F.R § 314.95" dated April 26, 2005

("the Notice"). The Notice states that the '358 patent is alleged to be not infringed, unenforceable, and/or invalid.

17. Defendants have infringed the '358 patent under Title 35, United States Code, § 271(c)(2)(A) by filing the ANDA.

18. Upon information and belief, Defendants presently use, offer for sale, and sell metformin in the U.S. and import metformin into the U.S.

19. Upon information and belief, some patients who take repaglinide for the treatment of NIDDM also take metformin for the same purpose.

20. Upon information and belief, upon approval of the ANDA, Defendants will use, offer for sale, and sell in the U.S. and import into the U.S. concurrently the repaglinide products that are the subject of the ANDA and metformin for the treatment of NIDDM. Such activities will infringe at least one of the claims of the '358 patent under Title 35. United States Code, § 271(a).

21. Upon information and belief, upon approval of the ANDA and the resulting sale in the U.S. by Defendants of repaglinide products that are the subject of the ANDA, others will use, offer for sale, or sell in the U.S., the repaglinide products that are the subject of the ANDA with metformin and will use such combination in the treatment of NIDDM. Such activities will infringe at least one of the claims of the '358 patent under Title 35, United States Code, § 271(a).

22. Upon information and belief, upon approval of its ANDA, Defendants will actively solicit others to use, offer for sale, or sell in the U.S., the repaglinide products that are the subject of the ANDA alone and

with metformin and to use such combination in the treatment of NIDDM. Such activities by Defendants will actively induce infringement of at least one of the claims of the '358 patent under Title 35, United States Code, § 271(b).

23. Upon information and belief, Defendants' infringement has been willful and deliberate in disregard of Novo Nordisk's lawful rights under the '358 patent, thus rendering this case "exceptional" as set forth in Title 35, United States Code, § 285.

24. The acts of infringement set forth above will cause Novo Nordisk irreparable harm for which it has no adequate remedy at law, and will continue unless FDA approval of the ANDA is stayed until the expiration of the '358 patent, and unless Defendants are preliminarily and permanently enjoined by this Court,

WHEREFORE, Novo Nordisk prays that this Court:

a. enter a judgment that U.S. Patent No. 6,677,358 is infringed by Defendants under Title 35, United States Code, § 271(e)(2);

b. stay FDA approval of the ANDA for at least thirty months;

c. order that any effective date of any approval of the repaglinide products that are the subject of the ANDA shall be a date which is not earlier than the date of the expiration of U.S. Patent No. 6,677,358.

d. enter a judgment that Defendants' manufacture, use, offer for sale, or sale in the United States or importation into the United States of the repaglinide products that are the subject of the ANDA will infringe and actively induce infringement of the '358

patent under Title 35, United States Code, §§ 271 (a) and (b);

e. enter a judgment that U.S. Patent No, 6,677,358 is not invalid and is enforceable;

f. enter a judgment that Defendants' infringement and active inducement of infringement under Title 35, United States Code, §§ 271 (a) and (b) by Defendants' manufacture, use, offer for sale, or sale in the United States or importation into the United States of the repaglinide products that are the subject of the ANDA will be willful;

g. enter a judgment that Defendants' activities have made this action an exceptional case under Title 35, United States Code, § 285;

h. issue a preliminary injunction enjoining and restraining Caraco, Sun and their respective officers, directors, agents, servants, employees and attorneys and those in active concert or participation with them, from the manufacture, use, offer for sale, or sale in the United States, or importation into the United States of the repaglinide products that are the subject of the ANDA;

i. issue a permanent injunction enjoining and restraining Caraco, Sun and their respective officers, directors, agents, servants, employees and attorneys and those in active concert or participation with them from the manufacture, use, offer for sale, or sale in the United States, or importation into the United States of the repaglinide products that are the subject of the ANDA and any other product that infringes or induces infringement of the U.S. Patent No. 6,677,358;

j. grant Novo Nordisk compensatory damages in an amount to be determined at trial including both pre-judgment and post-judgment interest;

k. award Novo Nordisk treble damages;

l. award Novo Nordisk its costs and attorneys' fees; and

m. grant Novo Nordisk such other and further relief as it may deem just and proper.

Dated: August 12, 2005

* * * *

[Signature Blocks Omitted]

* * * *

Filed: Sept. 14, 2005

[Exhibit A Reproduced at JA 65 - 96]

[Firm Name Omitted in Original]

Charles Guttman
Member of the Firm

Direct Dial 212.969.3180
cguttman@proskauer.com

October 5, 2006

VIA REGISTERED MAIL
RETURN RECEIPT REQUESTED

Novo Nordisk A/S
Novo Allé
DK-2880, Bagsvaerd
Denmark

Novo Nordisk, Inc.
100 College Road West,
Princeton, NJ 08540

Attn: Legal Counsel

Re: Notice of Certification Under 21 U.S.C. § 355(j)(2)(B)(ii) (§ 505(j)(2)(B)(ii) of Federal Food, Drug and Cosmetic Act) and 21 C.F.R. § 314.95

I. Caraco Pharmaceutical Laboratories Limited ("Caraco") of Detroit, Michigan, hereby certifies under 21 U.S.C. § 355(j)(2)(B)(ii) and 21 C.F.R. § 314.95(c)(1), to the following persons that it has filed an Abbreviated New Drug Application ("ANDA") for permission to sell Repaglinide Tablets, 0.5 mg, 1 mg, and 2 mg (Repaglinide Tablets) which is bioequivalent to Prandin®, Repaglinide Tablets, 0.5 mg, 1 mg, and 2 mg (Prandin).

1. Holder of New Drug Application (NDA 020741) for Prandin:

Novo Nordisk, Inc
100 College Road West,
Princeton, NJ 08540

2. Owner of US Patent No. 6,677,358 (the '358 Patent) listed in the Orange Book:

Novo Nordisk A/S
Novo Allé
DK-2880, Bagsvaerd
Denmark

II. Pursuant to 21 U.S.C. § 355(j)(2)(B)(ii) and 21 C.F.R. § 314.95(c)(l), the United States Food and Drug Administration has received an ANDA from Caraco containing any required bioavailability and/or bioequivalence data showing that Caraco's proposed product is bioequivalent to Prandin (Repaglinide Oral Tablet) that is the subject of NDA 020741. The ANDA was submitted under 21 U.S.C. § 355(j)(1) and 2(A) with a paragraph IV certification to obtain approval to engage in the commercial manufacture, use, or sale of oral repaglinide oral tablets before the expiration of the '358 patent which is listed in *Approved Drug Products with Therapeutic Equivalence Evaluation* ("Orange Book").

III. Pursuant to 21 C.F.R. § 314.95(c)(2), the ANDA filed by Caraco has been assigned ANDA No. 77-571 by the FDA.

IV. Pursuant to 21 C.F.R. § 314.95(c)(3), the established name for the proposed drug product is REPAGLINIDE; TABLET; ORAL.

V. Pursuant to 21 C.F.R. § 314.95(c)(4), the active ingredient for the proposed drug product is re-

paglinide. The strength and dosage forms of the proposed drug product are equivalent to 0.5 mg, 1 mg and 2 mg of repaglinide, in an oral, tablet form.

VI. Pursuant to 21 C.F.R. § 314.95(c)(5), the following patent has been listed in the Orange Book and is alleged to be not infringed, unenforceable, and/or invalid:

US Patent No. 6,677,358 (expires June 12, 2018).

VII. Caraco alleges, and has certified to the FDA, that in its opinion and to the best of its knowledge, the patent listed above is invalid, unenforceable, and/or not infringed by the commercial manufacture, use, or sale of the drug product described by Caraco's ANDA. Pursuant to 21 U.S.C. § 355(j)(2)(b)(ii) and 21 C.F.R. § 314.95(c)(6), Caraco's detailed statement of the legal and factual basis for the certification set forth in Caraco's ANDA is contained in the attached Appendix.

VIII. Pursuant to 21 C.F.R. § 314.95(c)(7), the undersigned is authorized to accept service of process on behalf of Caraco at the address indicated below:

Charles Guttman
Proskauer Rose LLP
1585 Broadway
New York, New York 10036

IX. Pursuant to 21 U.S.C. § 355(j)(5)(C), this notice letter includes an Offer of Confidential Access to Application. As required by § 355(j)(5)(C)(i)(III), Caraco offers to provide confidential access to certain information from its ANDA No. 77-571 for the sole and exclusive purpose of determining whether an infringement action referred to in § 355(j)(5)(B)(iii) should be brought.

Section 355(j)(5)(C)(i)(III) allows Caraco to impose restrictions "as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information." That provision also grants Caraco the right to redact its ANDA to remove any information of no relevance to any issue of patent infringement in response to a request for Confidential Access under this offer.

As permitted by statute, Caraco imposes the following terms and restrictions on its Offer of Confidential Access:

(1) Caraco will permit confidential access to certain information from its proprietary ANDA No. 77-571 to attorneys from one outside law firm representing the Innovator; provided, however, that such attorneys do not engage, formally or informally, in patent prosecution for the Innovator. Such information (hereinafter, "Confidential Caraco Information") shall be marked with the legend "CONFIDENTIAL".

(2) The attorneys from the outside law firm representing the Innovator shall not disclose any Confidential Caraco Information to any other person or entity, including the Innovator employees, outside scientific consultants, and/or other outside counsel retained by the Innovator, without the prior written consent of Caraco's outside litigation counsel, Proskauer Rose LLP.

(3) As provided by § 355(j)(5)(C)(i)(III) the Innovator's outside law firm shall make use of the Confidential Caraco Information for the sole and exclusive purpose of determining whether an action referred to in § 355(j)(5)(B)(iii) can be brought and for no other

purpose. By way of example only, the Confidential Caraco Information cannot be used to prepare or prosecute any future or pending patent application by the Innovator, or in connection with any filing to or communication with the FDA relating to Caraco's ANDA No. 77-571. The Innovator's outside law firm agrees to take all measures necessary to prevent unauthorized disclosure or use of the Confidential Caraco Information, and that all Confidential Caraco Information shall be kept confidential and not disclosed in any manner inconsistent with this Offer of Confidential Access.

(4) The Confidential Caraco Information disclosed is, and remains, the property of Caraco. By providing the Confidential Caraco Information, Caraco does not grant the Innovator and/or the Innovator's law firm any interest in or license for, the Confidential Caraco Information.

(5) The Innovator's law firm shall, within thirty-five (35) days from the date that it first receives the Confidential Caraco Information, return to Caraco's outside litigation counsel, Proskauer Rose LLP, all Confidential Caraco Information and any copies thereof. The Innovator's law firm shall return to Proskauer Rose LLP all Confidential Caraco Information before any infringement suit is filed by Novo Nordisk, if suit is commenced before this 35-day period expires. In the event that the Innovator opts to file suit, none of the information contained in or obtained from any Confidential Caraco Information that Caraco provides will be included in any publicly-available complaint or other pleading.

(6) Nothing in this Offer of Confidential Access shall be construed as an admission by Caraco regarding

the validity, unenforceability and/or infringement of any U.S. Patent. Further, nothing herein shall be construed as an agreement or admission by Caraco with respect to the competency, relevance, or materiality of any such Confidential Caraco Information, document, or thing. The fact that Caraco provides Confidential Caraco Information upon request of the Innovator shall not be construed as an admission by Caraco that such Confidential Caraco Information is relevant to the disposition of any issue relating to any alleged infringement of the '358 patent, or to the validity of that patent.

(7) The attorneys from the Innovator's outside law firm will acknowledge in writing their receipt of a copy of these terms and restrictions prior to production of any Confidential Caraco Information. Such written acknowledgement shall be provided to Caraco's outside litigation counsel, Proskauer Rose LLP.

(8) This Offer of Confidential Access shall be governed by the laws of the State of New York. Section 355(j)(5)(C)(i)(III) provides that any request for access that the Innovator makes under this Offer of Confidential Access "shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in [this] offer of confidential access" and that the "restrictions and other terms of [this] offer of confidential access shall be considered terms of an enforceable contract." Thus, to the extent that the Innovator requests access to Confidential Caraco Information, it necessarily accepts the terms and restrictions outlined above. Written notice requesting access under this Offer of Confidential Access should be made to:

Charles Guttman
Proskauer Rose LLP
1585 Broadway
New York, New York 10036
Tel: 212.969.3180
Fax: 212.969.2900

By providing this Offer of Confidential Access to Application, Caraco maintains the right and ability to bring a Declaratory Judgment action under 28 U.S.C. §§ 2201 *et seq.*, pursuant to 21 U.S.C. § 355(j)(5)(C).

It is hereby certified that a copy of this Notice, together with the Appendix, has been sent by Registered Mail, Return Receipt Requested, to Legal Counsel of:

Novo Nordisk A/S
Novo Allé
DK-2880, Bagsvaerd
Denmark

Novo Nordisk, Inc.
100 College Road West
Princeton, NJ 08540

Very truly yours,

_____

Charles Guttman
Proskauer Rose LLP
1585 Broadway
New York, New York 10036

APPENDIX OF DETAILED REASONS

The following constitutes Caraco's detailed statement of the factual and legal bases for Caraco's belief that US 6,677,358 (hereinafter, US '358) is not infringed by the commercial manufacture, use or sale of the drug product described in Caraco's ANDA. This detailed statement will not preclude Caraco from advancing any other grounds for invalidity, noninfringement, and/or unenforceability, or any other claim construction, of the '358 Patent in the event of litigation.

A. Innovator's Repaglinide Tablets and Label

Innovator's Prandin tablet contains repaglinide as the active ingredient in 0.5 mg, 1 mg and 2 mg strengths. The indications and usage in innovator's label includes indication as an adjunct to diet and exercise to lower the blood glucose in patients with type 2 diabetes mellitus and an indication for combination therapy use (with metformin or thiazolidinediones) to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise plus monotherapy with other agents.

B. Caraco's ANDA Drug Product and Label

The proposed drug product that is the subject of Caraco's ANDA No. 77-571 ("the ANDA drug product") is Repaglinide Tablets containing as the active ingredient repaglinide 0.5 mg, 1 mg and 2 mg. Caraco's proposed label does not include any indication for combination therapy with metformin.

C. The US '358 Patent and its Prosecution History

US '358, entitled "NIDDM Regimen," was issued to Novo Nordisk on January 13, 2004. US '358 is based upon U.S. App. No. 09/459,526, filed December 13, 1999, which is a continuation of PCT App. No. PCT/DK98/00248, filed June 12, 1998, which is based upon U.S. Prov. App. No. 60/063,368, filed in the PTO on October 29, 1997. US '358 also claims the benefit of priority of an application filed in Denmark on June 13, 1997. Assuming all maintenance fees are paid, US '358 is expected to expire on June 12, 2018, as listed in the Orange Book.

US '358 describes a combination therapy for the treatment of NIDDM (Non-Insulin Dependent Diabetes Mellitus). US '358 contains 5 claims, of which claims 1, 4, and 5 are independent. Claim 1 claims a pharmaceutical composition comprising repaglinide and metformin together with a suitable carrier. Claim 4 claims a method for treating NIDDM comprising administering to a patient repaglinide in combination with metformin. Claim 5 claims a kit for use in treatment of a patient having NIDDM, the kit comprising an amount of repaglinide and an amount of metformin.

As originally filed, not all of the claims in App. No. 09/459,526 were restricted to the combination of repaglinide and metformin. Rather, some of the original claims merely recited the administration of an effective amount of a short-acting hypoglycemic agent, while other claims recited the combination of a short-acting hypoglycemic agent and a long-acting hypoglycemic agent. However, during the course of prosecution, Novo restricted all claims in App. No.

09/459,526 to the specific combination of repaglinide and metformin in order to distinguish over the prior art. Additionally, Novo emphasized that the prior art cited by the Examiner did not disclose the specific combination of repaglinide and metformin for the treatment of NIDDM, and that this combination produces a "synergistic effect."

Based on the restriction of all claims to the combination of repaglinide and metformin and the arguments made by Novo including the submission of a Declaration Under 37 C.F.R. §1.132 of Dr. Sturis, the Examiner allowed the claims of US '358. In issuing a Notice of Allowance, the Examiner stated as Reasons for Allowance that "the present application is solely directed to the combination of repaglinide and metformin for use in treating non-insulin dependent diabetes mellitus," and that "the combined administration of repaglinide and metformin resulted in an unexpected synergistic effect on blood glucose levels," citing the Declaration of Dr. Sturis.

Accordingly, US '358 was issued on January 13, 2004, with its present set of claims all of which are restricted to the combination of repaglinide and metformin.

D. Comparison of Caraco's Repaglinide Tablets and Labeling with the Claims of US '358

The Court of Appeals for the Federal Circuit ("Federal Circuit") has repeatedly stated that direct infringement requires a two-step analysis. First, the claims of the patent in issue must be properly construed to determine their scope. Second, the accused device, product, or process must be compared to the properly construed claims. E.g., *Mars, Inc.* v. *H.J. Heinz Co.*, 377 F.3d 1369 (Fed. Cir. 2004); *Becton*

Dickinson & Co. v. *C.R. Bard, Inc.*, 922 F.2d 792 (Fed. Cir. 1990). Infringement is found if the accused device, product, or process contains each and every element, either literally or by a substantial equivalent, of at least one claim in the patent. E.g., *Charles Greiner & Co.* v. *Mari-Med. Mfg., Inc.*, 962 F.2d 1031 (Fed. Cir. 1992). Furthermore, it is not possible to infringe a dependent claim without infringing the independent claim from which it depends. *Wahpeton Canvas Co.* v. *Frontier, Inc.*, 870 F. 2d 1546 (Fed. Cir. 1989).

As recounted above, each of the independent claims in US '358 recites the specific combination of repaglinide and metformin. This includes claim 4 which claims a method for treating NIDDM comprising administering to a patient repaglinide in combination with metformin. The prosecution history described above demonstrates that the claims in US '358 were allowed only because they are restricted to this specific combination and Novo argued that this specific combination produces a synergistic effect.

Accordingly, by ascribing to the terms used in the independent claims of US '358 their plain and ordinary meanings as understood by a person of ordinary skill in the art, since such meanings do not create any ambiguities and since the specification and/or prosecution history do not clearly indicate that any different meanings are intended, the independent claims of US '358 must be construed as being restricted to the combination of repaglinide and metformin. Furthermore, the Doctrine of Prosecution History Estoppel precludes Novo from expanding the coverage of the claims to encompass anything which does not include this particular combination.

ANDA No. 77-571 of Caraco seeks approval to market Repaglinide Tablets alone and not in combination with metformin. Therefore, Caraco's product will not infringe claim 1 (directed to a pharmaceutical composition) and claim 5 (directed to a kit used in the treatment of a patient having NIDDM) of US '358.

With regard to claim 4 (directed to a method for treating NIDDM), Caraco's ANDA does not seek approval to market repaglinide in combination with metformin, and Caraco's proposed label does not contain any indication or reference to the treatment of NIDDM by administering repaglinide in combination with metformin. Specifically, there is no listing under "Indications and Usage" or under "Dosage and Administration" in Caraco's proposed label for the combination of repaglinide and metformin.

Accordingly, Caraco's filing of ANDA No. 77-571 will not directly infringe claim 4 of US '358 under 35 U.S.C. 271(e)(2)(A). See, *Warner Lambert Co.* v. *Apotex*, 316 F.3d 1348 (Fed. Cir. 2003).

With regard to active inducement of infringement of claim 4, the Federal Circuit in *Warner-Lambert* also noted that "mere knowledge alone of possible infringement by others is insufficient to prove inducement." Rather, "specific intent and action to induce infringement must be proven." In the absence of any evidence that the ANDA applicant has or will promote or encourage doctors to infringe a method of treatment patent, active inducement of infringement is not proven.

Thus, in *Warner-Lambert*, the Federal Circuit concluded that the mere filing of an ANDA does not constitute direct infringement or active inducement of infringement of a method-of-use patent where the

ANDA does not seek approval to market for the claimed use. As the Federal Circuit stated:

> "The ANDA must be judged on its face for what an accused infringer seeks the FDA's approval to do. Section 271(e)(2) does not encompass 'speculative' claims of infringement. The statute explicitly defines the act of infringement as the filing of the ANDA. The infringement case is therefore limited to an analysis of whether what the generic drug maker is requesting authorization for in the ANDA would be an act of infringement if performed."

The decision rendered in the *Warner-Lambert* case is binding and controlling law. Therefore, Caraco's filing of ANDA No. 77-571 which seeks approval to market Repaglinide Tablets but which does not seek approval to market repaglinide in combination with metformin for treatment of NIDDM, and which does not contain an indication in the proposed label for combination therapy with metformin, will not directly infringe and will not constitute an act of actively inducing infringement of claim 4 of US '358.

For the reasons given above, Caraco's Repaglinide Tablets and its ANDA for marketing of Repaglinide Tablets will not infringe any of the claims of US '358.

ANDA 77-571

Center for Drug Evaluation and Research-FDA
Office of Generic Drugs
Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: 301-827-9274

FAX TRANSMISSION COVER SHEET

DATE: 8/10/07

TO: APPLICANT: Caraco Pharm.
TEL: 313-556-4178

ATTN: Veeranna Lolla
FAX: 313-556-4199

FROM: Lisa Kwok
PROJECT MANAGER: 301-827-5739

TOTAL NUMBER OF PAGES: 5
(EXCLUDING COVER SHEET)

Special Instructions: Congratulations! Your application has been tentatively approved.

* * * *

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-571

Caraco Pharmaceuticals Laboratories, Ltd.
Attention: Derrick Mann
Director, Regulatory Affairs
1150 Elijah McCoy Drive
Detroit, MI 48202

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated February 9, 2005, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Repaglinide Tablets USP, 0.5 mg, 1 mg, and 2 mg.

Reference is also made to your amendments dated April 13, June 22, September 30, and November 22, 2006; April 3, June 13, November 22, and December 28, 2006; and April 13, and August 8, 2007.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the patent issue noted below. Therefore, the ANDA is tentatively approved. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to our attention. This let-

ter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The reference listed drug (RLD) upon which you have based your ANDA, Prandin, 0.5 mg, 1 mg, and 2 mg, of Novo Nordisk Pharmaceuticals, Inc., is subject to periods of patent protection. As noted in the agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"), U.S. Patent Nos. 6,677,358 (the '358 patent) and RE37035 (the '035 patent) are scheduled to expire on June 12, 2018 and March 14, 2009, respectively.

With respect to the '358 patent, your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that the patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Repaglinide Tablets USP, 0.5 mg, 1 mg, and 2 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Caraco Pharmaceutical Laboratories, Ltd. (Caraco) for infringement of a patent that was the subject of the paragraph IV certifications. This action must have been brought against Caraco prior to the expiration of 45 days from the date the notice you provided under section 505(j)(2)(B)(i) was received by the NDA/patent holder(s). You notified the agency that Caraco complied with the requirements of section 505(j)(2)(B) of the Act, and within the statutory 45-day timeframe litigation for infringement of the '358 patent was brought against Caraco in the U.S. Eastern Dist. of Michigan [Novo Nordisk Pharmaceuticals Inc. v. Ca-

raco Pharmaceuticals, Ltd., Civ. Action No. 05-40188].

Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii)

   b. the date the court decides[1] that the '358 patent is invalid or not infringed (see sections 505(j)(5)(B)(iii)(I), (II), and (III) of the Act), or

   c. the '358 patent has expired, and

2. The agency is assured there is no new information that would affect whether final approval should be granted.

With respect to the '035 patent, your ANDA contains a paragraph III certification under section 505(j)(2)(A)(vii)(III) of the Act stating that you will not market this drug product prior to the expiration of the '035 patent. Therefore, final approval of your application may not be made effective pursuant to section 505 of the Act until the '035 patent has expired, i.e., March 14, 2009.

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT – FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions

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[1] This decision may be either a decision of the district court or the court of appeals, whichever court is the first to decide that the patent is invalid or not infringed.

under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT – FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the Act. Also, until the agency issues the final approval letter,

this drug product will not be deemed to be approved for marketing under section 505 of the Act, and will not be listed in the "Orange Book."

For further information on the status of this application, or prior to submitting additional amendments, please contact Leigh Ann Matheny, Project Manager, at 301-827-9275.

Sincerely yours,

{*See appended electronic signature page*}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

* * * *

[Electronic Signature Page Omitted]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-741

RECEIVED

NOV 28 2007

Mary Ann McElligott

Novo Nordisk Inc
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prandin (repaglinide) Tablets.

Recently, the Division has been evaluating the professional labeling for all oral anti-diabetic drugs. There has been much public debate over the expected benefits of these drugs beyond their intended use for controlling hyperglycemia, as demonstrated by a reduction in the well-established surrogate, HbA1c. In addition, the treatment of type 2 diabetes mellitus is highly individualized and selection of any particular approved drug, its use as a single agent or as combination therapy, and the timing of initiating monotherapy versus combination therapy should be based on many factors that should be left to the discretion of the healthcare provider (e.g., baseline HbA1c, concurrent medical conditions, safety profile of the drug).

Consequently, the Division is requesting changes to the professional labeling of all oral anti-diabetic drugs

to appropriately reflect the findings of efficacy and safety of these products and to better inform prescribers when selecting an oral anti-diabetic drug for their patients. The following sections of the label should be modified as described below:

1. Under **CLINICAL STUDIES**

Add a statement at the beginning of this section describing how this drug has been studied. Include a statement listing the major classes of anti-diabetic drugs that have not been studied in combination with your drug, but which are likely to be used in combination with your drug (e.g., sulfonylureas, insulin, etc.).

"Prandin has been studied as monotherapy and in combination with Drug A, B, and C. Prandin has not been studied in combination with Drug A, B, and C."

2. Under **INDICATIONS AND USAGE**

Replace all the separate indications (e.g., monotherapy, combination therapy, and initial or second-line therapy) with the following sentence:

"Prandin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus."

3. Under **PRECAUTIONS**

Add the following statement to reflect the absence of macrovascular outcome data for all oral anti-diabetic drugs:

"There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Prandin or any other oral anti-diabetic drug."

Submit draft labeling as a prior approval supplement to this application within 60 days.

Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made. Please note, the labeling changes outlined in this letter do not require revising the package insert to the Physician's Labeling Rule (PLR) format.

Your response must also include updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

If you have any questions, call Julie Marchick, Regulatory Project Manager, at 301-796-1280

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

* * * *

[Electronic Signature Page Omitted]

CARACO
PHARMACEUTICAL LABORATORIES, LTD.

TELEPHONE AMENDMENT

April 02, 2008

Via Fax and Courier

Attn.: Jim Barlow
Division of Labeling and Program Support
Labeling Review Branch
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Telephone Amendment to ANDA #77-571 for Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg.

Caraco Pharmaceutical Laboratories Ltd. (Caraco) hereby submits a Telephone Fax Labeling Amendment for the drug product Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg in response to letter received on March 17, 2008 from Jim Barlow, Labeling Reviewer, Office of Generic Drugs, CDER, FDA. A copy of the FDA letter is enclosed.

Pursuant to 21 CFR 314.96, we hereby amend our application with information regarding labeling changes. Attached please find our response to the Labeling deficiencies.

Two copies of this labeling amendment have been provided, one Archival copy and one for Review.

If you have any questions, please free to contact me at (313) 556 4178.

Sincerely,

/s/ Veeranna Lolla
Veeranna Lolla, RAC
Sr. Manager, Regulatory Affairs

Enclosures

* * * *

[Electronic Signature Page Omitted]

Caraco Pharmaceutical Laboratories, Ltd.
Labeling Amendment to ANDA # 77-571
Repaglinide Tablets USP, 0.5 mg, 1 mg and 2 mg

Labeling Deficiencies:

1. **GENERAL COMMENT:**

a. You provided a PIV certification for patent#..358 that expires 2018. If you wish to exclude text regarding "the combination use with metformin" (U-546) and include other information pertaining to other claims within patent #..358, then you may split the patent certification. This would allow you to paragraph IV some information and MOU other information (e.g., "metformin information"). Please provide a revised patent certification specifying what your wishes are.

b. Delete the following from the text of your labels and labeling- Important Notice: U.S. patent law may restrict the use of repaglinide in combination with metformin. If you wish to use this product in combination with metformin, you should use Prandin®-brand repaglinide. See package outsert for full details.

Response:

a. Caraco Pharmaceutical Laboratories Ltd. (Caraco) acknowledges the Agency's comment regarding PIV certification to the patent#..358. Based upon Agency's recommendation, Caraco revised the patent certification to the patent#..358 and hereby submitting split certification which allows us to carve out the information pertaining to use of Repaglinide in combination with Metformin.

The revised patent certifications are included in **Attachment 1**.

b. Caraco has revised the outsert labeling and container labels to delete the information regarding "Important Notice: U.S. patent law may restrict the use of repaglinide in combination with metformin. If you wish to use this product in combination with metformin, you should use Prandin®-brand repaglinide. See package outsert for full details."

To support the above change the following documents are included:

- A side-by-side comparison of the proposed package outsert (Iss. 03/08) against the reference listed drug Prandin® (Iss. 06/06) with differences annotated and explained as **Attachment 2**.

- A side-by-side comparison of proposed container labels (Iss. 03/08) against the previously submitted labels (Iss. 10/07) with differences annotated and explained in **Attachment 3**.

The proposed package outsert and container labels for Repaglinide Tablets USP, 0.5 mg, 1 mg and 2 mg in Final Printed Labeling format is submitted electronically on a CD-ROM as **Attachment 4**.

2. CONTAINER (100s, 500s, and 1000s):

See above comments

Response: Please refer to the response under General Comment

3. OUTSERT:

See above comments

Response: Please refer to the response under General Comment

Electronic Labeling

The electronic submission of the labeling is included in a CD-ROM, consistent with the Guidances for Industry entitled "Providing Regulatory Submissions in Electronic Format-Content of Labeling" (Issued 4/2005) as **Attachment 4**. This submission is organized in a Portable Document Format (.pdf) comprising the following:

Table of Contents: This .pdf file lists all examples of labeling included in the submission, providing a hypertext link between the documents listed in the table of contents and the corresponding PDF file and a bookmark for each item in the table of contents.

- **History pi:** This .pdf file includes the list of the labeling changes for the outsert proposed in the submission and the explanation of changes.
- **History label:** This .pdf file includes the list of the labeling changes for the labels proposed in the submission and the explanation of changes.
- **RLD pi:** This .pdf file includes Approved RLD, Iss. 06/06.
- **Proposed pi (Iss. 03/08):** This .pdf file includes proposed labeling for the outsert, Iss. 03/08.

- **Proposed label (Iss. 03/08):** This .pdf file includes proposed labeling for the container labels, Iss. 03/08.

- **Proposed label (Iss. 10/07):** This .pdf file includes proposed labeling for the container labels, Iss. 10/07.

The content of outsert labeling in **XML** format is organized in a folder entitled **'spl'**.

To facilitate the review, the electronic labeling also includes the proposed outsert labeling in MS Word format.

ATTACHMENT 1

SUGGESTED STATEMENTS OF CERTIFICATION UNDER SECTION 505(j)(2)(A)(viii) AND 21 CFR 314.94(a)(12)

A. Patent Certification [Section 505(j)(2)(A)(vii) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.94(a)(12)]

Enclosed in this section is the statement of patent certification for Caraco's ANDA for **Repaglinide Tablets, 0.5 mg, 1 mg and 2 mg**.

These statements are in accordance with the Federal Food, Drug and Cosmetic Act, as amended December 8, 2003 (Prescription Drug and Medicare Improvement Act of 2003) and with the Code of Federal Regulations as amended and effective March 10, 2004.

1. Paragraph III Certification for U.S. Patent No. RE37035

In accordance with the Federal Food, Drug, and Cosmetic Act, as amended December 8, 2003, Patent Certification is hereby provided for our Abbreviated New Drug Application for **Repaglinide Tablets, 0.5 mg, 1 mg and 2 mg**.

CARACO PHARMACEUTICALS LABORATORIES. LTD. hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. RE37035, ***will expire*** **on Mar 14, 2009** which is the expiration date listed in the Orange Book for this patent.

CARACO PHARMACEUTICALS LABORATORIES. LTD. will not market the drug product until the U.S. Patent No. RE37035 has expired.

CARACO PHARMACEUTICAL LABS. LTD.

/s/ Robert Kurkiewicz — 04-02-08
Robert Kurkiewicz — Date
Senior Vice President,
Regulatory Affairs
Caraco Pharmaceutical
Laboratories, Ltd.
1150 Elijah McCoy Drive
Detroit, MI 48202

Revised on 04/02/2008

2. Paragraph IV Certification for U.S. Patent No. 6,677,358

In accordance with the Federal Food, Drug, and Cosmetic Act, as amended December 8, 2003, Patent Certification is hereby provided for our Abbreviated New Drug Application for **Repaglinide Tablets 0.5mg, 1mg and 2 mg**.

CARACO PHARMACEUTICAL LABS LTD. hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. **6,677,358**, which as per the expiration date listed in the Orange Book for this patent will expire on June 12, 2018, is ***invalid, unenforceable or will not be infringed*** by the manufacture, use or sale of **Caraco's Repaglinide Tablets 0.5mg, 1mg and 2mg** for which this application is submitted.

CARACO PHARMACEUTICAL LABS LTD.

/s/ Robert Kurkiewicz — 04-02-08
Robert Kurkiewicz — Date
Senior Vice President,
Regulatory Affairs
Caraco Pharmaceutical
Laboratories, Ltd.
1150 Elijah McCoy Drive
Detroit, MI 48202

Revised on 04/02/2008

2. Paragraph IV Certification for U.S. Patent No. 6,677,358 (continued)

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.94(a)(12)(i)(A)(4) and 21 CFR 314.95, CARACO PHARMACEUTICALS LABORATORIES. LTD. hereby states that, upon receipt from the FDA of an acknowledgment letter stating that this ANDA is sufficiently complete to permit a substantive review, it has provided the notice required by Section 505(j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.95 to Novo Nordisk A/S, Bagsvaerd (DK), owner of U.S. Patent No. 6,677,358, and to Novo Nordisk Pharmaceuticals, Inc., 100 College Road West, Princeton, NJ 08540, the holder of the NDA for PRANDIN® (Repaglinide oral tablet) vide letter dated Apr 26, 2005.

This notice to Novo Nordisk, (Dk) and to Novo Nordisk Pharmaceuticals Inc, NJ, which was sent by certified mail, return receipt requested, and re-

ceived by them on May 9, 2005 met the requirements of 21 CFR 314.95(a) and 21 CFR 314.95(c).

CARACO PHARMACEUTICAL LABS. LTD.

/s/ Robert Kurkiewicz — 04-02-08
Robert Kurkiewicz — Date
Senior Vice President,
Regulatory Affairs
Caraco Pharmaceutical
Laboratories, Ltd.
1150 Elijah McCoy Drive
Detroit, MI 48202

Revised on 04/02/2008

3. Statement under Section 355(j)(2)(A)(viii) and CFR 314.94(a)(12)(iii)(A) for U.S. Patent No. 6,677,358

In accordance with the Federal Food, Drug, and Cosmetic Act, as amended December 8, 2003, Patent Certification is hereby provided for our Abbreviated New Drug Application for **Caraco's Repaglinide tablets, 0.5mg, 1mg and 2mg**.

CARACO PHARMACEUTICAL LABS LTD. hereby certifies that with reference to U.S. Patent No. 6,677,358 (which expires on June 12, 2018, as per the Orange Book) and to the extent that it is a method-of-use patent, Caraco (the applicant) does not seek approval for use of Repaglinide in combination with Metformin to lower blood glucose (as specified under U-546 listed against U.S. Patent No. 6,677,358).

CARACO PHARMACEUTICAL LABS. LTD.

/s/ Robert Kurkiewicz — 04-02-08

Robert Kurkiewicz — Date

Senior Vice President,
Regulatory Affairs
Caraco Pharmaceutical
Laboratories, Ltd.
1150 Elijah McCoy Drive
Detroit, MI 48202

Revised on 04/02/2008

Stipulation Regarding Case Issues And Scheduling

Sun/Caraco has advised Novo Nordisk that it intends to change its certification and label submitted to the FDA with its ANDA. As of the date of this Stipulation, Novo Nordisk has not received nor reviewed the new, amended certification or label. Accordingly, Novo Nordisk enters into this Stipulation without waiver or prejudice to any rights, remedies, positions or motions that may be available or appropriate with regard to the amended certification or label.

In exchange for all of the covenants below, the parties hereby agree and stipulate as follows:

1. Sun/Caraco stipulates that Caraco's submission of its ANDA infringes the '358 patent to the extent it (a) includes a label that discusses the combination of metformin and repaglinide, or contains information concerning combination therapy that includes the metformin-repaglinide combination; and (b) does not include a disclaimer approved by the FDA in substantially the same form as what Caraco requested in its letter dated October 16, 2007 – i.e., a disclaimer addressing Novo Nordisk's patent protection under the '358 patent. Sun/Caraco further stipulates that any use, manufacture, sale, offer to sell or distribution of repaglinide pursuant to Caraco's ANDA also infringes the '358 patent to the same extent indicated above. This Stipulation shall not be deemed an admission as to Sun/Caraco's intent with regard to any other label.

2. The parties request that the Court schedule a Rule 16 status conference in May 2008, or as soon thereafter as the Court's schedule permits to discuss the pre-trial schedule, pre-trial submissions and the trial setting. At the status conference, dates for the

exchange of expert reports, expert discovery cut off and dispositive motions will be discussed and set.

3. Fact discovery shall be extended through the status conference referenced in Paragraph 2. The final close of fact discovery will be addressed at that status conference, but in no event will the close of fact discovery occur prior to 75 days from the date Sun/Caraco lodges with the FDA and serves Novo Nordisk with its new amended label and certification referenced in the preamble above or June 30, 2008 – whichever is later. If, at the end of this period, the Court has not set a fact discovery cut off date or has not ruled on any pending requests to continue or terminate fact discovery, fact discovery will continue until such time as the Court rules.

4. Pursuant to Paragraph 5(b) of the Stipulated Protective Order, Sun/Caraco agrees to permit Novo Nordisk to use, in communications with the FDA regarding Caraco's ANDA, all Sun/Caraco's correspondence with the FDA regarding Caraco's ANDA, including but not limited to, documentation submitted to the FDA, electronic mail with the FDA and any records of communications with the FDA. No other use of such documents by Novo Nordisk, other than that provided for in the Protective Order, shall be permitted at this time.

5. Novo Nordisk agrees that it will submit any and all Citizen Petition(s) concerning Caraco's ANDA within 60 days from the date Sun/Caraco lodges with the FDA and serves Novo Nordisk with its new amended label and certification. Novo Nordisk shall retain the right to comment and respond to any action taken by the FDA concerning such Citizen Petition(s). Following the 60 day period, Novo Nordisk

agrees not to file any new Citizen Petition(s) with the FDA concerning Caraco's ANDA, except if (a) the FDA allows a different label change other than the one that will be requested by Sun/Caraco as part of its new certification referenced above; (b) Sun/Caraco makes another amendment to its ANDA other than the one that will be requested by Sun/Caraco as part of its new certification referenced above; or (c) the Citizen Petition solely addresses facts that Novo Nordisk did not know, and, through the exercise of reasonable diligence, could not have known, at the time of the stipulation (other than final approval of Caraco's ANDA).

6. Novo Nordisk agrees to withdraw its current motion to amend the scheduling order without prejudice.

STIPULATED AND AGREED TO BY:

/s/ Josh A. Krevitt
Josh A. Krevitt
John L. LaBarre
GIBSON, DUNN & CRUTCHER LLP
200 Park Avenue
New York, NY 10166-0193

Michael Sitzman
GIBSON, DUNN & CRUTCHER LLP
One Montgomery Street
Post Montgomery Center
San Francisco, CA 94104-4505

Counsel for Plaintiffs/Counterclaim Defendants, Novo Nordisk A/S and Novo Nordisk Inc.

/s/ Charles B. Klein
David S. Bloch
WINSTON & STRAWN LLP
101 California Street
San Francisco, CA 94111-5802

Charles B. Klein
WINSTON & STRAWN LLP
1700 K Street, N.W.
Washington, DC 20006-3817

Counsel for Defendants/Counterclaim Plaintiffs, Caraco Pharmaceutical Laboratories, Ltd. and Sun Pharmaceutical Industries, Ltd.

Dated as of: April 8, 2008

Filed: April 28, 2008

Novo Nordisk

June 9, 2008

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BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Approval of Abbreviated New Drug Applications for Repaglinide

Dear Sir or Madam:

CITIZEN PETITION

Novo Nordisk Inc. ("Novo Nordisk") submits this petition pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act ("FDC Act"), among other provisions of law, and 21 C.F.R. § 10.30. Novo Nordisk, through this petition, respectfully requests that the Food and Drug Administration ("FDA") refrain from approving any abbreviated new drug application ("ANDA") for repaglinide that omits crucial information on metformin combination therapy, which is protected by patent and currently appears in the labeling of the innovator product, PRANDIN®.

As discussed in more detail below, PRANDIN is approved, both as monotherapy and for use in combination with metformin or thiazolidinediones ("TZDs"), as an adjunct to diet and exercise to lower the blood glucose in patients with type 2 diabetes, also known as non-insulin dependent diabetes mellitus ("NIDDM"). The PRANDIN labeling contains, as it has since the drug was first approved in 1997, extensive information related to its use in combination with metformin. Omission of this critical information

would render a generic repaglinide less safe and/or effective than PRANDIN, and any ANDA with labeling that omits such information relating to combination use with metformin should not be approved by FDA.

Novo Nordisk has filed this petition because at least one ANDA applicant, Caraco Pharmaceuticals Laboratories, Ltd. ("Caraco"), has received tentative approval for an ANDA (No. 77-751) for generic repaglinide.[1] At the time of tentative approval, Caraco's labeling included metformin combination therapy information. Caraco has since proposed labeling that omits such information. Novo Nordisk is concerned that FDA will grant final approval for the repaglinide ANDA with labeling that omits the metformin combination therapy information – an action that would result in insufficient and misleading information being provided to physicians prescribing generic repaglinide, to pharmacists dispensing the drug, and to patients using the drug.

A. ACTION REQUESTED

Novo Nordisk requests that FDA refrain from approving any ANDA, including ANDA No. 77-751 submitted by Caraco, for repaglinide that is not labeled for both monotherapy and combination therapy in the same manner as is PRANDIN. This includes any repaglinide ANDA whose labeling omits reference to metformin combination therapy in any section of the labeling, regardless of the content of other sec-

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[1] *See* Press Release, "Caraco Pharmaceutical Laboratories, Ltd. Announces Tentative FDA Approval for Generic Prandin(R)," available at http://phx.corporate-ir.net/phoenix.zhtml?c=98920&p=irol-newsArticle Print&ID=1039802&highlight= (Aug. 13, 2007).

tions of the labeling.

B. STATEMENT OF GROUNDS

1. Background

Novo Nordisk has rights to repaglinide in the United States, where it markets and distributes repaglinide under the trademark PRANDIN®.[2] PRANDIN is an oral blood glucose-lowering drug of the meglitinide class and is used in the management of type 2 diabetes. PRANDIN was originally approved by FDA in 1997 with an indication that included both monotherapy and combination therapy with metformin: (1) as an adjunct to diet and exercise to lower blood glucose in patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily controlled with diet and exercise alone; and (2) for use in combination with metformin to lower blood glucose in patients whose hyperglycemia cannot be controlled by exercise, diet, and either repaglinide or metformin alone. PRANDIN is currently approved for use in monotherapy or combination therapy (with metformin or TZDs) essentially for the single indication of lowering blood glucose in those suffering from type 2 diabetes.

Recently, FDA "has been evaluating the professional labeling for all oral anti-diabetic drugs ["OADs"]."[3] FDA has recognized that the "selection of

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[2] PRANDIN® is a registered trademark of Novo Nordisk A/S and is used under license by Novo Nordisk. Recently, Novo Nordisk has entered into an agreement allowing Sciele Pharmaceuticals, Inc. to market repaglinide in the United States.

[3] *See* Letter from Mary H. Parks, M.D., Director, Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, Center for Drug Evaluation and Research, to Mary Ann McElligott, Ph.D., Novo Nordisk Inc. (Nov. 21, 2007).

any particular approved [OAD], its use as a single agent or as combination therapy, and the timing of initiating monotherapy versus combination therapy" is a highly individualized process that should be left to the discretion of the type 2 diabetes patient's healthcare provider. Accordingly, FDA issued a directive to revise the professional labeling of all OADs (the "FDA Directive"). The FDA Directive requires, among other things, the revision of the *Indications and Usage* section of all labeling for all OADs to a single, straightforward statement that encompasses all therapy regimens for the drug. Among other things, the FDA Directive indicates that Novo Nordisk should submit revised labeling that "[r]eplace[s] all the separate indications (e.g., monotherapy, combination therapy, and initial or second-line therapy) with [the statement] 'Prandin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.'" Novo Nordisk has complied with the FDA Directive. Under the proposed labeling submitted by Novo Nordisk in response to the FDA Directive, the discussion of PRANDIN in combination with metformin still remains in the labeling, including a discussion in the *Clinical Trials* and *Dosage and Administration* sections. In its 11-year history as an approved drug, PRANDIN has never been approved exclusively as a monotherapy or for any use other than those in the current PRANDIN labeling.

Novo Nordisk is the holder of the approved new drug application ("NDA") for PRANDIN. The Orange Book lists two patents for PRANDIN: U.S. Patent No. RE 37,035 ("the '035 patent") that claims, *inter alia*, the chemical composition of repaglinide and expires on March 14, 2009, and U.S. Patent No. 6,677,358

("the '358 patent") that claims, *inter alia*, repaglinide in combination with metformin and expires on June12, 2018.[4]

Initially, Caraco made a paragraph III certification with respect to the '035 patent[5] and a paragraph IV certification with respect to the '358 patent.[6] The paragraph IV certification as to the '358 patent stated that the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of repaglinide tablets by Caraco under its ANDA. Under the provisions of the Drug Price Competition and Patent Term Restoration Act, Novo Nordisk commenced a lawsuit against Caraco on June 9, 2005, which was within the forty-five day period following Caraco's notice to Novo Nordisk of the paragraph IV certification. This lawsuit is currently pending as *Novo Nordisk A/S and Novo Nordisk Inc.* v. *Caraco Pharmaceutical Laboratories, Ltd. and Sun Pharmaceutical Industries, Ltd.*, Civ. Action No. 4:05-cv-40188 (E.D. Mich.).

Over the course of the last three years, Caraco has amended its proposed labeling multiple times to try

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[4] More specifically, the '358 patent contains 5 claims, one of which (claim 4) is directed to a method of treatment of NIDDM with a combination of repaglinide and metformin. The remaining claims of the '358 patent are directed towards either a pharmaceutical composition containing both repaglinide and metformin (claims 1-3) or to a kit comprised of at least repaglinide and metformin (claim 5).

[5] *See* 21 U.S.C. § 355(j)(2)(A)(vii)(III). Consideration of this petition should not result in delay of approval by FDA of an otherwise approvable ANDA for repaglinide because final approval cannot be effected until March 14, 2009, when the '035 patent expires.

[6] *See id.* § 355(j)(2)(A)(vii)(IV).

to avoid infringement of the '358 patent and obtain approval from FDA. Caraco received tentative approval on labeling that includes the metformin combination usage but has subsequently tried to remove such information. In its penultimate attempt, Caraco proposed a patent disclaimer with exculpatory language relating to the '358 patent. On March 16, 2008, FDA denied this request. In response, Caraco has now amended its ANDA to revise its certification with respect to the '358 patent to also include, a section viii statement[7] that it is not seeking approval for the method of use claimed by the '358 patent (i.e., that it is not seeking approval for a method of treating type 2 diabetes with a repaglinide/metformin combination).[8] Caraco's labeling amendment does not

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[7] *See id.* § 355(j)(2)(A)(viii).

[8] The allowance of a split certification with respect to a single patent appears to run counter to FDA practice. As explained in *Purepac Pharm. Co.* v. *Thompson*, 354 F.3d 877, 885-86 (D.C. Cir. 2004) in reviewing the lower court history:

> [T]he court reviewed the FDA's post-Purepac decision against making an exception to its longstanding rule that for every patent only one of two approaches--a section viii statement or a paragraph IV certification--is appropriate. Although the FDA had indicated in Purepac that on remand it would consider granting an exception to this rule by accepting TorPharm's paragraph IV certification, the agency ultimately decided against such an exception, deeming the certification improper. The district court found this decision neither arbitrary nor capricious, explaining that the refusal "to make an equitable exception from this rule was within the FDA's discretion, and TorPharm has pointed to nothing in the statute or regulations to cast doubt on the rule itself." Recognizing the narrow scope of review, the district court concluded that the FDA's rule deserved judicial deference "in the absence of some indication that it conflicts with any of the constraints on the

exclude all combination use; just the most widely prescribed combination use with metformin. Each of Caraco's amendments, including this most recent request, was made for litigation purposes, and without regard for the implications of withholding relevant information on the safety and efficacy of Caraco's generic repaglinide product.

Reflecting anticipated medical use of the drug, the initial labeling for PRANDIN contained information based on studies demonstrating safety and effectiveness when PRANDIN was used both as monotherapy and in combination with metformin, the primary drug used in the treatment of type 2 diabetes when PRANDIN was initially approved.[9] FDA's approval in 2002 of a supplement to the PRANDIN NDA resulted in the addition to the labeling of information pertaining to the use of repaglinide in combination with TZDs. The information on use of repaglinide as combination therapy is not limited to the *Indications and Usage* section of the labeling, but appears pervasively throughout the labeling, including the *Clinical Trials* and *Dosage and Administration* sections. This is not a situation in which two unrelated indications were

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agency's regulatory authority, is inconsistent with the agency's own prior pronouncements, or is otherwise poorly reasoned or unpersuasive. There are no such indications here." TorPharm gives us no basis for questioning the district court's sound reasoning. (internal citations omitted).

[9] *See* Declaration of Silvio E. Inzucchi, M.D. ¶ 31 ("Inzucchi Decl.") (attached as Exhibit 1). Dr. Inzucchi is a prominent endocrinologist and Professor of Medicine at Yale University School of Medicine. Dr. Inzucchi has executed a declaration in support of this Citizen Petition based on his education, training, and experience with regard to the treatment of patients with type 2 diabetes.

evaluated separately by FDA, each on its own merits; rather, the information pertaining to the use of repaglinide as monotherapy and in combination with metformin is intertwined and, given the progressive nature of type 2 diabetes, represents the anticipated medical practice for the drug.

2. Analysis

a. A Section viii Statement is Inappropriate under Either the Current Labeling or the Labeling as it Will be Revised in Accordance with the FDA Directive.

As discussed above, Caraco recently amended its ANDA to include a section viii statement with respect to the '358 patent in addition to its paragraph IV certification. A section viii statement is appropriate where an applicant is seeking approval to market a drug for a limited subset of all uses for which the reference drug has been approved.[10] In this case, a section viii statement is not appropriate since repaglinide is effectively approved only for a single use – the treatment of type 2 diabetes.

This is true under both the current PRANDIN labeling and the proposed revised PRANDIN labeling in accordance with the FDA Directive. The original approval of PRANDIN was for a single indication that included monotherapy together with combination use with metformin as part of an approved continuum of use for achieving glycemic control. This indication was later expanded to include combination use with TZDs, and the current PRANDIN indication includes monotherapy, combination use with metformin, and combination use with a TZD. That the com-

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[10] 21 U.S.C. § 355(j)(2)(A)(viii).

bination use with metformin is an integral part of the indication was made even more clear by the FDA Directive instructing Novo Nordisk to merge the uses of PRANDIN into a single indication.[11] To the extent that it was unclear under the current PRANDIN labeling, it is unequivocal in the proposed labeling for PRANDIN that the only indication for which repaglinide will be approved will be the treatment of type 2 diabetes. As there will only be a single indication for PRANDIN, there is no additional indication or use that can be carved out by a section viii statement. Consequently, since a section viii statement is only appropriate in circumstances where there are multiple indications or uses and where the applicant is seeking marketing approval for only a subset of those approved indications or uses, a section viii statement is not appropriate under either the current labeling or the revised labeling.

This very question has been addressed by both FDA and United States District Court for the District of Columbia as discussed in *Purepac Pharma. Co.* v. *Thompson.*[12] In that case, Purepac was seeking approval of a drug for which the FDA had only approved a single use, namely the treatment of epilepsy. In attempting to gain approval to market the drug from FDA, Purepac had submitted a section viii statement with respect to a method of treatment patent that had been listed for the drug in the Orange Book. FDA

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[11] Caraco's proposed labeling can only be based on the currently approved PRANDIN labeling. We raise the issue of the labeling supplement Novo Nordisk has submitted in accordance with the FDA Directive because we expect this labeling supplement to be approved during the pendency of this Citizen Petition.

[12] 238 F. Supp. 2d 191 (D.D.C. 2002) (affirmed *Purepac Pharm. Co.* v. *Thompson*, 354 F.3d 877 (D.C. Cir. 2004)).

denied the request on the grounds that a section viii statement is inappropriate where the use for which Purepac sought approval (treatment of epilepsy) was the same as was covered by the patent.[13] As the *Purepac* court stated in recounting FDA's position denying the section viii statement: "[A] section viii statement was inappropriate because the use for which Purepac sought approval was the same as the use that must have been claimed by the patent in question."[14] In other words, where a drug has only one approved use, a section viii statement is simply not appropriate.[15] Ultimately, the *Purepac* court went on, however, to overturn FDA's finding with respect to the patent-in-suit's inclusion in the Orange Book (i.e., it found that the patent-in-suit was inappropriately listed in the Orange Book because it covered an off-label use and was not related to the treatment of epilepsy). There is no such argument in the current matter relating to the appropriateness of the inclusion of the '358 patent in the Orange Book.

The FDA's basic logic and analysis with respect to gabapentin applies in this matter. Under either the current labeling or any labeling revised pursuant to the FDA Directive relating to OAD labeling, there is only a single approved use for PRANDIN (i.e., the treatment of type 2 diabetes). There is no alternative approved method of treating that can be carved out by a section viii statement. In other words, a section viii statement is only appropriate in circumstances where there are multiple indications or uses and

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[13] *Id.* at 199-200.

[14] *Id.* at 200.

[15] *See id.* at 208 (explaining the FDA's position with respect to a section viii statement on a product for which there was only one approved use).

where the applicant is seeking marketing approval for only a subset of approved indications or uses.

In this instance, as there is only one approved use, a section viii statement is not appropriate. Accordingly, FDA should not approve an ANDA for repaglinide that includes labeling with a carve-out such as that proposed by Caraco.

b. Omission of Metformin Combination Therapy Information Would Render Generic Repaglinide Less Safe and Less Effective for the Remaining, Non-protected Conditions of Use.

Labeling that omits reference to the use of repaglinide in combination with metformin would substantially affect the safety of a generic repaglinide product in contradistinction to the FDC Act and should be rejected by FDA. The FDC Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]" and "information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug...."[16] The FDC Act provides the following two exceptions for when ANDA labeling may differ from that of the listed drug: (1) when changes reflect differences approved pursuant to an ANDA suitability petition or (2) when the drugs are produced or distributed by different manufacturers.[17] FDA regulations implementing the statutory exceptions to the ANDA labeling requirement state that "differences

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[16] 21 U.S.C. § 355(j)(2)(A)(i), (v).

[17] *Id.* § 355(j)(2)(A)(v).

between the applicant's proposed labeling and labeling approved for the reference listed drug may include . . . omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the [FDC Act]."[18] The regulations further provide that to approve an ANDA that omits an aspect of labeling protected by patent or exclusivity, FDA must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."[19] In the preamble to the final rule, FDA explains that "it will not approve an ANDA with different labeling if the labeling differences affect product safety or efficacy."[20]

The FDC Act and FDA's implementing regulations do not permit FDA to approve an ANDA for repaglinide that does not contain the information related to use of repaglinide in combination with metformin because, as discussed in detail below, such omission would render generic repaglinide less safe and effective than PRANDIN for its non-protected conditions of use.

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[18] 21 C.F.R. § 314.94(a)(8)(iv).

[19] *Id.* § 314.127(a)(7). Novo Nordisk does not challenge FDA's general authority to permit "carve-outs" of protected information in certain circumstances, authority that has been recognized in court decisions. *See, e.g., Sigma-Tau Pharmaceuticals, Inc.* v. *Schwetz*, 288 F.3d 141 (4th Cir. 2002); *Bristol-Myers Squibb Co.* v. *Shalala*, 91 F.3d 1493 (D.C. Cir. 1996). Rather, Novo Nordisk asserts, as described in more detail below, that carving out the combination therapy use of repaglinide is inappropriate because it does not meet the requirements of 21 C.F.R. § 314.124(a)(7).

[20] 57 Fed. Reg. 17,950, 17,968 (Apr. 28, 1992).

i. Permitting a Generic to Carve Out the Use of Repaglinide with Metformin Would Result in the Omission of Important Information.

Type 2 diabetes is a complex, multi-system, and increasingly common metabolic disease that causes premature morbidity and mortality worldwide.[21] It is a progressive disease that typically necessitates progressive treatment.[22] In that regard, the current PRANDIN labeling notes:

> The effectiveness of any hypoglycemic drug in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of diabetes or to diminished responsiveness to the drug.[23]

Many patients progress from monotherapy to combination therapy, for example, by adding repaglinide to a metformin regimen or by adding metformin or another antidiabetic agent to a repaglinide regimen.[24] The optimal clinical approach is predicated on the information available to the experienced physician and his or her understanding of the characteristics of each agent, how it works, and what side effects to expect.[25] A high percentage of patients taking repaglinide do so in combination with at least one other OAD; the most commonly prescribed combination therapy for patients taking repaglinide is with met-

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[21] Inzucchi Decl. ¶ 16.

[22] *Id.* ¶ 24.

[23] PRANDIN Prescribing Information, *Precautions, Loss of Control of Blood Glucose*. A copy of this labeling is attached as Exhibit 2.

[24] Inzucchi Decl. ¶¶ 34-36.

[25] *Id.* ¶ 35.

formin.

The labeling of a generic repaglinide product that sought to carve out the combination therapy information protected by the '358 patent would not contain the following crucial information:

- the effective use of repaglinide as an adjunct to metformin monotherapy in the treatment of type 2 diabetes;
- the effective use of repaglinide in combination with metformin when repaglinide monotherapy is insufficient in the treatment of type 2 diabetes;
- results of clinical studies of repaglinide and metformin in the treatment of type 2 diabetes; and
- the dose-sparing effects of repaglinide/metformin combination therapy.

Without such information, a generic repaglinide product cannot be as safe or effective as PRANDIN. Indeed, as highlighted below, certain information found in the PRANDIN labeling is essential to the safe and effective use of the approved drug.

First, the *Clinical Trials* section of the PRANDIN labeling describes a study in which repaglinide was co-administered with metformin to patients not satisfactorily controlled on exercise, diet, and metformin alone. The combination study demonstrated significantly greater improvement in glycemic control by patients taking the combination as compared to repaglinide or metformin monotherapy.[26] The combination study also demonstrated dose-sparing effects with respect to repaglinide when taken in combina-

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[26] PRANDIN Prescribing Information, *Clinical Trials*.

tion with metformin.[27]

Second, the *Dosage and Administration* section of the PRANDIN labeling instructs the patient and the physician when to use combination therapy and what to do if hypoglycemia results in order to assure safety and effectiveness. It provides that:

> If PRANDIN monotherapy does not result in adequate glycemic control, metformin or a thiazolidinedione may be added. If metformin or thiazolidinedione monotherapy does not provide adequate control, PRANDIN may be added.
>
> * * * * * [In original]
>
> When hypoglycemia occurs in patients taking a combination of PRANDIN and a thiazolidinedione or PRANDIN and metformin, the dose of PRANDIN should be reduced.[28]

Third, the *Information for Patients* section of the PRANDIN labeling warns that: "Patients should be informed of the potential risks and advantages of PRANDIN and of alternate modes of therapy."[29] It further states that:

> The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development and concomitant administration of other glucose-lowering drugs [*i.e.*, com-

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[27] *Id.*

[28] *Id., Dosage and Administration, Combination Therapy, Patient Management.*

[29] *Id., Information for Patients.*

bination therapy] should be explained to patients and responsible family members.[30]

Repaglinide is increasingly used in combination with metformin.[31] Dr. Inzucchi, a leading diabetes practitioner, indicates that potentially more than half of the patients who are prescribed PRANDIN are also prescribed metformin to be taken concurrently.[32] Moreover, those patients who are treated initially with repaglinide as monotherapy will almost invariably require combination therapy with another antidiabetic agent at some point in time.[33] The converse is also true; those patients who are treated initially with metformin as monotherapy will almost invariably require combination therapy with another antidiabetic agent at some point in time.[34] Patients, physicians, and pharmacists, in the normal course of treatment of type 2 diabetes, will be expected to use repaglinide in combination with other type 2 diabetes drugs, whether or not repaglinide was used by the patient as monotherapy.

Labeling that omits discussion of repaglinide used in combination with metformin ignores the progressive nature of the medical treatment of these patients.[35] Patients, physicians, and pharmacists, in or-

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[30] *Id.*

[31] Inzucchi Decl. ¶ 37.

[32] *Id.* ¶ 38.

[33] *Id.* ¶¶ 37-38.

[34] *Id.* ¶ 38.

[35] *See id.* ¶¶ 34-40. For purposes of illustration, for every 10 prescriptions for generic repaglinide as monotherapy, there will be up to 5 prescriptions for generic repaglinide in combination with metformin. Thus, a significant portion of the medical community will prescribe and dispense, and a significant portion of the type 2 diabetes patient population will receive, repaglinide for treat-

der to decide whether or when monotherapy or combination therapy is indicated and to decide how to use repaglinide safely and effectively, must be advised in the labeling of the drug about the use of repaglinide in combination with other hypoglycemic agents, adjustments that can be made to counter adverse events, and relevant studies of combination therapy. The omission of such information is likely to mislead physicians, pharmacists, and patients as to the safety and efficacy of such drugs. Neither the safety of repaglinide nor its potential effectiveness can be best described without information on combination use with metformin in the labeling.

ii. Permitting a Generic to Carve Out the Use of Repaglinide with Metformin Will Lead to Less Safe and Less Effective Treatment Options for Type 2 Diabetes Patients.

Carving out from the repaglinide labeling the use of repaglinide in combination with metformin would have several undesirable consequences that may lead to less safe and effective treatment options.

First, the absence of a repaglinide/metformin combination from the labeling could create the false impression that the two drugs should not be used in combination with each other. Not only is such an impression incorrect, it is also contrary to documented scientific studies which have demonstrated a dramatic benefit to the use of repaglinide in combination with metformin.[36]

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ing type 2 diabetes, but without complete effectiveness and safety information on that treatment. *Id.* ¶ 41.

[36] *See, e.g.*, Moses, "Combination Therapy in Type 2 Diabetes: The Role of Repaglinide," JAPI, Vol. 49, pp. 62-68 (January 2001); Raskin, et al., "Efficacy and Safety of Combination Ther-

Second, because such labeling would still indicate combination of repaglinide with TZDs, such labeling would imply that the only approved combination therapy would be the use of repaglinide in combination with TZDs. While TZDs are effective drugs for the treatment of type 2 diabetes for many patients, there are a number of warnings or precautions associated with the TZDs that are not present with metformin. Discussion of the most significant follows:

(i) the labeling for the marketed TZDs, ACTOS® (pioglitazone hydrochloride) and AVANDIA® (rosiglitazone maleate), both have black box warnings linking TZD use with congestive heart failure in some patients.[37] AVANDIA's black box warning also discusses a meta-analysis that showed AVANDIA to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction, though the boxed warning also states that the available data on the risk of myocardial ischemia, in their entirety, are inconclusive.[38] Metformin does not have any such warnings related to congestive heart failure or myocardial ischemic events;

(ii) the labeling for the TZDs contains a precaution that dose-related weight gain was observed with

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apy – Repaglinide Plus Metformin Versus Nateglinide Plus Metformin," Diabetes Care, Vol. 7, pp. 2063-68 (July 2003); Rudovich, et al., "Enhancement of Early- and Late-Phase Insulin Secretion and Insulin Sensitivity by the Combination of Repaglinide and Metformin in Type 2 Diabetes Mellitus," Exp Clin Endocrinol Diabetes, 112(7), pp. 395-400 (July 2004).

[37] *See* ACTOS and AVANDIA Prescribing Information. Copies are attached as Exhibits 3 and 4.

[38] AVANDIA also has a Medication Guide that discusses these and other risks.

> TZDs alone or in combination with other hypoglycemic agents.[39] While the mechanism of action for the weight gain was unclear, the labeling states that it was likely related to a combination of fluid retention and fat accumulation. Patients with rapid weight gain should be assessed for fluid overload states, including congestive heart failure. Metformin has no such precaution related to weight gain.

These warnings and precautions related to the use of TZDs, which are not present for the use of metformin, demonstrate that carving out the use of repaglinide in combination with metformin may render the product less safe for the remaining non-protected conditions of use.[40]

Third, metformin side effects include diarrhea, nausea, vomiting, gas, weakness, indigestion, and abdominal discomfort.[41] The use of metformin in combination with repaglinide may result in lower initial dosages of metformin and a resulting lower incidence of such side effects.[42] The absence of labeling support for repaglinide/ metformin combination usage is likely to result in higher dosages of metformin when taken as a monotherapy, even in those patients who are susceptible to metformin's side effects, where combination treatment at lower dose ranges would otherwise be sufficient.

Finally, by eliminating the data and information pertaining to the use in combination with metformin,

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[39] *See* ACTOS and AVANDIA Prescribing Information.

[40] *See* Inzucchi Decl.¶ 43.

[41] *Id.* ¶ 32

[42] *Id.*

the generic repaglinide labeling also eliminates the safe and effective use of repaglinide in combination with both metformin *and a TZD*, which for many patients, is a more effective option than repaglinide in use with a TZD alone.[43]

c. FDA Precedent Requires Refusal to Approve ANDAs for Repaglinide Without Critical Combination Therapy Labeling.

In accordance with its statutory and regulatory provisions, FDA has recently granted a citizen petition requesting relief similar to that requested by Novo Nordisk in this petition. Specifically, FDA granted the petition submitted by Wyeth Pharmaceuticals ("Wyeth") requesting that FDA refrain from approving any generic versions of RAPAMUNE (sirolimus) that omitted critical information pertaining to cyclosporine before the expiration date of statutory exclusivity for protected information.[44] In that case, FDA concluded that the omission of information pertaining to a cyclosporine withdrawal clinical study contained in the *Pharmacokinetics, Clinical Studies, Indications and Usage, Warnings, Precautions,* and *Adverse Reactions* sections of the labeling and which resulted in three years of marketing exclusivity for Wyeth, would render the product less safe for the remaining, non-protected conditions of use. FDA noted that the protected labeling "contains extensive, critical prescribing information pertaining to cyclosporine withdrawal that any physician should receive to ap-

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[43] *Id.* ¶42.

[44] *See* Letter from Steven K. Galson, M.D., M.P.H., Acting Director, Center for Drug Evaluation and Research, to Michael S. Labson, Covington & Burling, Docket No. 2003P-0518/CP1 (Sept. 20, 2004).

propriately determine treatment for all indications of sirolimus."[45] As the continued use of cyclosporine would not be an acceptable maintenance regimen in renal transplant patients at low to moderate risk for rejection, which represent the majority of the renal transplant patient recipients in the U.S., FDA determined that "approving an ANDA for sirolimus without the cyclosporine withdrawal language, thereby limiting the indication to the remaining narrow subset of renal transplant patients at high risk for rejection, could be potentially unsafe and confusing."[46]

The same is true for repaglinide. FDA must consider that, as discussed above, it is clear that many PRANDIN monotherapy patients progress to combination therapy, and the majority of patients currently taking repaglinide do so in combination with some other OAD such as metformin.[47] Therefore, even though some patients begin their type 2 diabetes drug therapy with repaglinide or metformin alone, most will ultimately be treated by some form of combination therapy. The lack of information in a generic repaglinide's labeling about usage in combination with metformin, as FDA concluded with respect to RAPAMUNE, would render the generic product less safe, less effective, and confusing in light of the innovator drug labeling, which includes information relating to combination with metformin.

A review of recent FDA determinations permitting ANDA applicants to carve out certain protected information in order to obtain approval for those products demonstrates why omitting the protected infor-

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[45] *Id.* at 3.

[46] *Id.* at 4.

[47] *See* Inzucchi Decl. ¶ 38.

mation in this case would render generic repaglinide less safe or effective for the remaining conditions of use.

FDA's reasoning behind its determination that geriatric labeling protected by three-year marketing exclusivity could be carved out of the labeling for generic oxandrolone products supports the present petitioner's position that combination therapy cannot be carved out of the generic repaglinide labeling.[48] Regarding oxandrolone, FDA agreed that the omission of geriatric information was permissible because "generic oxandrolone products would be as safe and effective as OXANDRIN for all of these indications if the new geriatric use information were omitted, because the concerns addressed in the new OXANDRIN geriatric labeling apply within the general adult population (not just the geriatric population) and are, as a result, adequately addressed by the labeling applicable to all adults."[49] Moreover, FDA noted that there was no factual basis to assert that the geriatric labeling was necessary to the product's safety and effectiveness because oxandrolone had been on the market for over 40 years and had not shown evidence of safety or effectiveness concerns peculiar to the geriatric population.[50] None of the oxandrolone saving properties exists with PRANDIN.

The information that would be deleted from the generic repaglinide labeling (e.g., information advis-

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[48] *See* Letter from Steven K. Galson, M.D., M.P.H., Director, Center for Drug Evaluation and Research, to Edward John Allera, Buchanan Ingersoll P.C., Docket No. 2005P-0383 (Dec. 1, 2006) ("Galson Oxandrin Letter").

[49] *Id.* at 16.

[50] *Id.* at 17.

ing the physician, pharmacist, and patient of the progressive therapy regimen typically required for type 2 diabetes treatment, the effectiveness of repaglinide in combination use with metformin, and the dose-sparing effects of combination use with metformin) informs the physician, pharmacist, and patient about the full range of effectiveness of the drug product and the related safety concerns. The information sought to be deleted from the repaglinide generic labeling is not applicable to all of the repaglinide patient population at the same time. Repaglinide can be administered in different ways (i.e., alone or in combination) to treat type 2 diabetes. This distinguishes the repaglinide information that is proposed to be deleted from the generic labeling from the deleted oxandrolone information that was simultaneously applicable to the geriatric and non-geriatric patient population. Furthermore, oxandrolone had been on the market for over 40 years without the geriatric information (as noted above), whereas, in this case, the repaglinide labeling has always carried information pertaining to combination therapy with metformin. Thus, the oxandrolone determination demonstrates why no metformin combination therapy information should be carved out from the generic repaglinide labeling – carving out the metformin combination therapy information from the repaglinide labeling would be confusing and would make generic repaglinide less safe and effective than the innovator drug.

Similarly, FDA's determination with regard to REBETOL (ribavirin) supports the argument that FDA should refuse any request to omit combination therapy information from generic repaglinide labe-

ling.[51] In the ribavirin situation, FDA permitted generic applicants to omit labeling referring to combination use of ribavirin with the drug PEG-INTRON (peginterferon alpha-2b). FDA concluded that this information could be omitted because the generic products would still be labeled for combination use with another related product from the same family of drugs as PEG-INTRON, INTRON A, and remain safe and effective. FDA stressed that its ribavirin determination was product-specific.

With regard to PRANDIN, the drugs identified in the labeling for use in combination with PRANDIN are not related drugs from the same family. The PRANDIN labeling contains information about combination therapy with metformin and with TZDs. Metformin is not chemically or pharmacologically related to any other class of oral antihyperglycemic agents.[52] Metformin, a commonly prescribed drug for type 2 diabetes, is a biguanide, not a TZD.[53] The exact mechanism of action of metformin is unknown, but it reduces the liver's production of glucose.[54]

TZDs, on the other hand, lower glucose by reducing insulin resistance ("insulin sensitizers"), primarily in fat and muscle, but also to some degree in the liver.[55] "This effect occurs through the binding of the drug to a receptor inside the nucleus of the cell,

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[51] Letter from Steven K. Galson, M.D., M.P.H., Acting Director, Center for Drug Evaluation and Research, to David M. Fox, Hogan & Hartson, L.L.P. Docket No. 2003P-0321/CP1 (Apr. 6, 2004).

[52] Inzucchi Decl. ¶ 31.

[53] *Id.*

[54] *Id.*

[55] *Id.* ¶ 33.

known as 'PPAR-gamma.'"[56] "Binding to PPAR-gamma results in its activation, and subsequently, the production of a variety of proteins by the cells that affect glucose metabolism."[57] "The net result is to allow, under the direction of insulin, more glucose inside the cell and out of the blood stream. TZDs improve a cell's sensitivity to insulin."[58] Members of this class of drugs are TZD derivatives, including rosiglitazone (AVANDIA), pioglitazone (ACTOS), and troglitazone (REZULIN, withdrawn from the market in 2000). TZDs are commonly used in combination therapy, including in combination with repaglinide.[59] The omission of metformin combination therapy labeling will omit an entire class of combination therapy drugs and in fact, the most prescribed class of type 2 diabetes drugs. Clearly this omission would be confusing and affect safety and efficacy.

Finally, FDA's determination with regard to ULTRAM (tramadol) further illuminates why FDA should refuse any request to omit the metformin combination therapy information from labeling for generic repaglinide.[60] In that case, FDA permitted the generic applicant to omit protected titration labeling because unprotected titration labeling that would serve the same purpose as the protected labeling was available. Therefore, neither the effectiveness nor the safety of generic ULTRAM was affected. There is no

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[56] *Id.*

[57] *Id.*

[58] *Id.*

[59] *Id.*

[60] Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to Marcy Macdonald, et al., Docket Nos. 01P-0495/CP1, 02P-0191/CP1, & 02P-0252/CPI. (June 11, 2002).

similar unprotected labeling available for generic repaglinide. Metformin is a unique type 2 diabetes drug in its activity and in its ubiquity in the treatment of type 2 diabetes. Omission of metformin combination therapy information available for generic repaglinide would greatly affect a significant portion of the type 2 diabetes patient population, and thereby adversely affect the effectiveness and safety of the drug. As such, the FDA cannot authorize such omission.

d. Approval of an ANDA for Repaglinide without Metformin Would Compromise the Requirement for a Listed Drug and Create a New Drug Never Evaluated by FDA for Safety and Effectiveness.

One of the principal requirements for the content of an ANDA is that it contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the [ANDA drug] have been previously approved for a [listed drug]."[61] Repaglinide has never been approved exclusively as a monotherapy and has always been concurrently approved for combination use with metformin. ANDAs that seek approval of a generic form of repaglinide exclusively as a monotherapy or as combination therapy that excludes metformin would fail to contain information relating to how any repaglinide labeling has previously been approved.[62] In short, it is inappropriate to remove one of the approved com-

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[61] 21 U.S.C. § 355(j)(2)(A)(i).

[62] The subsequent approval of a supplement to add the use of PRANDIN in combination with a TZD to the indication does not affect the analysis that the original approved indication cannot be cleaved of its metformin component to permit approval of a generic labeled for use as monotherapy by itself or with a TZD.

bination uses (in fact, the predominant use) of PRANDIN from the labeling of generic repaglinide as Caraco proposes. The PRANDIN labeling requested in the FDA Directive does not change this analysis. It merely subsumes all treatment regimens into a single indication. Thus, under either the current labeling or the proposed labeling, the conditions of use sought by Caraco have not been previously approved for a listed drug that can serve as the basis for the subsequent approval of repaglinide for monotherapy use alone or in combination without metformin.

The fact that repaglinide was never approved for monotherapy alone renders 21 C.F.R. § 314.127 inapplicable. The fact that aspects of the listed drug's originally approved labeling may be subject to patent or other exclusivity protection does not authorize FDA to undertake new safety or effectiveness assessments of the listed drug under 21 C.F.R. § 314.127(a)(7). Rather, the safety and effectiveness test under this provision can only be applied in situations where the ANDA under review first meets the requirement that the proposed conditions of use have been previously approved for the listed drug. In other words, Caraco is seeking approval of generic repaglinide that is not indicated for use with metformin; however, such a product (i.e., labeled without metformin combination usage) has never been approved by FDA, and thus, no such product should be allowed now. Any other reading of this regulation would put it in conflict with the controlling statutory provision (21 U.S.C. § 355(j)(2)(A)(i)) and render it invalid.

Novo Nordisk recognizes that the issues presented here may not have been evaluated before due to the unique considerations of the progressive nature of type 2 diabetes. In this case, FDA has only approved

a course of therapy that includes both monotherapy and combination therapy, with information pertaining to both monotherapy and combination therapy woven throughout the labeling. Accordingly, Novo Nordisk submits that it is impossible to remove the metformin combination use of PRANDIN from the labeling of generic repaglinide and still adhere to the requirements of 21 U.S.C. § 355(j)(2)(A)(i).

Neither the *Bristol-Myers Squibb* case nor recent citizen petition responses counsels a different result.[63] In the *Bristol-Myers Squibb* case, Bristol-Myers Squibb had received initial approval and five year non-patent exclusivity for its drug for the treatment of hypertension. It subsequently obtained supplemental approvals for two new indications, each of which received separate three-year non-patent exclusivity. The first supplemental indication was for left ventricular dysfunction following myocardial infarction, and the second supplemental indication was for diabetic nephropathy in patients with type 1 insulin-dependent diabetes mellitus. The three indications *were for separate diseases, disease states, or conditions*, and the first approved indication did not include the second or third indications.

The present situation concerning Caraco's expected request to carve metformin combination ther-

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[63] *See Bristol-Myers Squibb Co.* v. *Shalala*, 91 F.3d 1493 (D.C. Cir. 1996); Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to Victor Raczkowski, M.D., Solvay Pharmaceuticals, Inc., Docket No. FDA-2007-P-0169 (Apr. 25, 2008) ("Woodcock Dronabinol Letter"); Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to William C. Bertrand, Jr., MedImmune Oncology, Inc., Docket No. 2006P-0410/CP1 (Mar. 13, 2008) ("Woodcock Amifostine Letter").

apy from its repaglinide labeling is not similar to that in the *Bristol-Myers Squibb* case. To avoid infringing Novo Nordisk's patent, Caraco proposes to remove a large portion of the original labeling and *sole disease indication* for PRANDIN, i.e., therapy for type 2 diabetes. This is not permitted under the statute and regulations. What is permitted is removal of a supplemental indication for a different disease. The information relating to that different disease theoretically would not affect the effectiveness or safety of the drug's use in the first disease. This reasoning is inapplicable to a drug whose sole use is for the treatment of the single disease, type 2 diabetes, and whose pertinent patient population includes numerous patients who require combination therapy with metformin, a use that was always part of the approved labeling for PRANDIN.

FDA's recent determinations with regard to dronabinol and amifostine present the same issues as the *Bristol-Myers Squibb* case and do not counsel a different result. In the dronabinol and amifostine situations, FDA stated that it would permit generic versions of the drugs to carve out protected indications when the omissions would not render the products less safe or effective for the remaining non-protected indications. With regard to dronabinol, FDA found that carving out information related to the protected AIDS indication would not render the product less safe or effective for the non-protected indication for the treatment of nausea and vomiting associated with cancer chemotherapy for patients who have failed to respond adequately to conventional treatments.[64] The company was concerned that generic dronabinol

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[64] Woodcock Dronabinol Letter, at 12.

would be prescribed off-label for the protected AIDS indication, leaving patients prescribed dronabinol for the AIDS indication without important information related to the use of the product in that indication. FDA stated that it could not consider the potential off-label use of the product in the protected AIDS indication in evaluating the citizen petition.[65] The same arguments were made and rejected by FDA with regard to amifostine.[66] The situation with repaglinide is quite different from both the dronabinol and amifostine cases. As discussed above, the use of repaglinide in combination with metformin is not a separate indication; carving out the use of repaglinide in combination with metformin would render repaglinide less safe or effective for the remaining conditions of use.

The *Bristol-Myers Squibb* court was also concerned that the innovator was trying to use the ANDA labeling regulations to "evergreen" its regulatory exclusivity.[67] That is not the case in the present situation. PRANDIN had one period of regulatory exclusivity as a new chemical entity. PRANDIN no longer has any regulatory exclusivity, and Novo Nordisk is not suggesting that any regulatory exclusivity should attach to PRANDIN due to indications and information for metformin combination therapy. Whether Novo Nordisk has applicable patent rights is an independent question that is presently under consideration in federal court. Here, FDA is asked to consider Novo Nordisk's contention that the generic repaglinide product would be rendered less safe and effective as PRANDIN for the non-protected condi-

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[65] *Id.* at 13-14.

[66] Woodcock Amifostine Letter, at 12-14.

[67] *See Bristol-Myers Squibb*, 91 F.3d at 1500.

tions of use in the absence of the metformin combination therapy information in the generic labeling.

e. Conclusion.

For the reasons discussed above, Novo Nordisk strongly believes that it would be contrary to the law and applicable regulations for FDA to approve any ANDAs for repaglinide that did not include the approved PRANDIN labeling describing the use of repaglinide in combination with metformin or TZDs. Any such approvals would provide inadequate and misleading information to prescribing physicians and to patients and would ultimately put patients at risk. Additionally, a section viii statement is not appropriate in these circumstances where the original approved indication was monotherapy together with metformin as part of a labeled continuum of use for achieving glycemic control. Moreover, the proposed PRANDIN labeling submitted in light of the FDA Directive, which provides for a single, merged indication for repaglinide, makes it even more clear that the use of repaglinide in combination with metformin cannot be carved out and that a section viii statement is therefore inappropriate. Any labeling proposed by a generic repaglinide applicant, including Caraco, that omitted combination use with metformin would be wholly inconsistent with the PRANDIN labeling. The motivation for seeking approval of such labeling could only be a desperate attempt to avoid infringement of Novo Nordisk's '358 patent, regardless of any issues that omission of the critical information might create with regard to the safe or effective use of generic repaglinide.

C. ENVIRONMENTAL IMPACT

A claim for categorical exclusion from the requirements for an Environmental Assessment is made under 21 C.F.R. § 25.31(a).

D. ECONOMIC IMPACT

An economic impact statement will be submitted at the request of the Commissioner.

E. CERTIFICATION

The undersigned certifies that, to my best knowledge and belief: (a) this petition includes all information and views on which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about August 2007 when the tentative approval for Caraco's repaglinide ANDA was announced. I further certify that the November 21, 2007, letter from FDA regarding required changes to the PRANDIN labeling; documents recently received in the pending patent litigation, *Novo Nordisk A/S and Novo Nordisk Inc.* v. *Caraco Pharmaceutical Laboratories, Ltd. and Sun Pharmaceutical Industries, Ltd.*, Civ. Action No. 4:05 CV 40188 (E.D. Mich.); and information recently made known to Novo Nordisk by its outside counsel provided additional support for the necessity of the action requested herein. I have not received, nor do I expect to receive, payments, including cash and other forms of consideration, to file this information or its contents

(other than compensation from my employer, Novo Nordisk, in the regular course of my employment). I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

/s/ Rosemarie R. Wilk-Orescan
Rosemarie R. Wilk-Orescan
Senior Counsel
Novo Nordisk Inc.

cc: Wm. Peter Rickman
Director – Division of Labeling
and Program Support
Office of Generic Drugs
CDER, FDA

NDA 20-741/S-034 Prandin Approval Letter

From: Marchick, Julie [Julie.Marchick@fda.hhs.gov]

Sent: Monday, July 14, 2008 3:04 PM

To: SSIK (Sabina Sheikh)

Subject: NDA 20-741/S-034 Prandin Approval Letter

Attachments: Approval Letter.pdf

Hi Sabina,

Attached is the approval letter for the Prandin supplement. <<Approval Letter.pdf>>

Julie

Julie Marchick
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301-796-1280 (phone)
301-796-9712 (fax)
julie.marchick@fda.hhs.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-741/S-034

Novo Nordisk Inc.
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, New Jersey 08540

Dear Dr. McElligott:

Please refer to your supplemental new drug application dated January 11, 2008, received January 11, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prandin (repaglinide) Tablets.

We acknowledge receipt of your submission dated July 11, 2008.

This supplemental new drug application provides for the following changes to the Package Insert, which were requested in a supplement request letter dated November 21, 2007.

1. The INDICATIONS AND USAGE section was changed to "PRANDIN is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus."

2. The following statement was added to the PRECAUTIONS section: "Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with PRANDIN or any other anti-diabetic drug."

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, submitted July 11, 2008). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 20-741/S-034."

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Julie Marchick, Regulatory Project Manager, at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

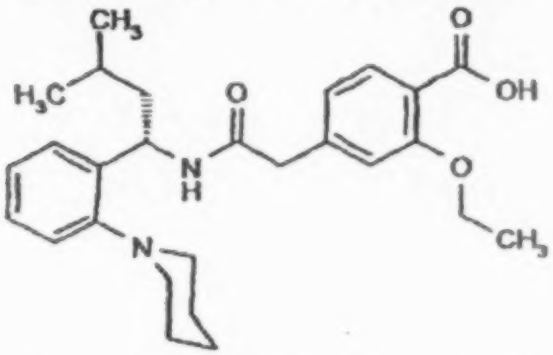
Enclosure: Package Insert

PRANDIN®
(repaglinide) Tablets (0.5, 1, and 2 mg)
Rx only

DESCRIPTION

PRANDIN® (repaglinide) is an oral blood glucose-lowering drug of the meglitinide class used in the management of type 2 diabetes mellitus (also known as non-insulin dependent diabetes mellitus or NIDDM). Repaglinide, S(+)2-ethoxy-4(2((3-methyl-1-(2-(1-piperidinyl) phenyl)- butyl) amino)-2-oxoethyl) benzoic acid, is chemically unrelated to the oral sulfonylurea insulin secretagogues.

The structural formula is as shown below:



Repaglinide is a white to off-white powder with molecular formula C_{27} H_{36} N_2 O_4 and a molecular weight of 452.6. PRANDIN tablets contain 0.5 mg, 1 mg, or 2 mg of repaglinide. In addition each tablet contains the following inactive ingredients: calcium hydrogen phosphate (anhydrous), microcrystalline cellulose, maize starch, polacrilin potassium, povidone, glycerol (85%), magnesium stearate, meglumine, and poloxamer. The 1 mg and 2 mg tablets contain iron oxides (yellow and red, respectively) as coloring agents.

CLINICAL PHARMACOLOGY

Mechanism of Action

Repaglinide lowers blood glucose levels by stimulating the release of insulin from the pancreas. This action is dependent upon functioning beta (ß) cells in the pancreatic islets. Insulin release is glucose-dependent and diminishes at low glucose concentrations.

Repaglinide closes ATP-dependent potassium channels in the ß-cell membrane by binding at characterizable sites. This potassium channel blockade depolarizes the ß-cell, which leads to an opening of calcium channels. The resulting increased calcium influx induces insulin secretion. The ion channel mechanism is highly tissue selective with low affinity for heart and skeletal muscle.

Pharmacokinetics

Absorption: After oral administration, repaglinide is rapidly and completely absorbed from the gastrointestinal tract. After single and multiple oral doses in healthy subjects or in patients, peak plasma drug levels (C_{max}) occur within 1 hour (T_{max}). Repaglinide is rapidly eliminated from the blood stream with a half-life of approximately 1 hour. The mean absolute bioavailability is 56%. When repaglinide was given with food, the mean T_{max} was not changed, but the mean C_{max} and AUC (area under the time/plasma concentration curve) were decreased 20% and 12.4%, respectively.

Distribution: After intravenous (IV) dosing in healthy subjects, the volume of distribution at steady state (V_{ss}) was 31 L, and the total body clearance (CL)

was 38 L/h. Protein binding and binding to human serum albumin was greater than 98%.

Metabolism: Repaglinide is completely metabolized by oxidative biotransformation and direct conjugation with glucuronic acid after either an IV or oral dose. The major metabolites are an oxidized dicarboxylic acid (M2), the aromatic amine (M1), and the acyl glucuronide (M7). The cytochrome P-450 enzyme system, specifically 2C8 and 3A4, have been shown to be involved in the N-dealkylation of repaglinide to M2 and the further oxidation to M1. Metabolites do not contribute to the glucose-lowering effect of repaglinide.

Excretion: Within 96 hours after dosing with ^{14}C-repaglinide as a single, oral dose, approximately 90% of the radiolabel was recovered in the feces and approximately 8% in the urine. Only 0.1% of the dose is cleared in the urine as parent compound. The major metabolite (M2) accounted for 60% of the administered dose. Less than 2% of parent drug was recovered in feces.

Pharmacokinetic Parameters: The pharmacokinetic parameters of repaglinide obtained from a single-dose, crossover study in healthy subjects and from a multiple-dose, parallel, dose-proportionality (0.5, 1, 2 and 4 mg) study in patients with type 2 diabetes are summarized in the following table:

Parameter	Patients with type 2 diabetes[a]
Dose	$AUC_{0\text{-}24\ hr}$ Mean±SD (ng/mL*hr):
0.5 mg	68.9 ± 154.4
1 mg	125.8 ± 129.8
2 mg	152.4 ± 89.6
4 mg	447.4 ± 211.3

Dose	$C_{max0\text{-}5\ hr}$ Mean ±SD (ng/mL):
0.5 mg	9.8 ± 10.2
1 mg	18.3 ± 9.1
2 mg	26.0 ± 13.0
4 mg	65.8 ± 30.1
Dose	$T_{max0\text{-}5\ hr}$ Means (SD)
0.5 - 4 mg	1.0 - 1.4 (0.3 - 0.5) hr
Dose	$T_{1/2}$ Means (Ind Range)
0.5 - 4 mg	1.0 - 1.4 (0.4 - 8.0) hr
Parameter	**Healthy Subjects**
CL based on i.v.	**38 ± 16 L/hr**
V_{ss} based on i.v.	**31 ± 12 L**
AbsBio	**56 ± 9%**

a: dosed preprandially with three meals

CL = total body clearance
V_{ss} = volume of distribution at steady state
AbsBio = absolute bioavailability

These data indicate that repaglinide did not accumulate in serum. Clearance of oral repaglinide did not change over the 0.5 - 4 mg dose range, indicating a linear relationship between dose and plasma drug levels.

Variability of Exposure: Repaglinide AUC after multiple doses of 0.25 to 4 mg with each meal varies over a wide range. The intra-individual and inter-individual coefficients of variation were 36% and 69%, respectively. AUC over the therapeutic dose range included 69 to 1005 ng/mL*hr, but AUC exposure up to 5417 ng/mL*hr was reached in dose escalation studies without apparent adverse consequences.

Special Populations:

Geriatric: Healthy volunteers were treated with a regimen of 2 mg taken before each of 3 meals. There were no significant differences in repaglinide pharmacokinetics between the group of patients <65 years of age and a comparably sized group of patients ≥65 years of age. (See **PRECAUTIONS, Geriatric Use)**

Pediatric: No studies have been performed in pediatric patients.

Gender: A comparison of pharmacokinetics in males and females showed the AUC over the 0.5 mg to 4 mg dose range to be 15% to 70% higher in females with type 2 diabetes. This difference was not reflected in the frequency of hypoglycemic episodes (male: 16%; female: 17%) or other adverse events. With respect to gender, no change in general dosage recommendation is indicated since dosage for each patient should be individualized to achieve optimal clinical response.

Race: No pharmacokinetic studies to assess the effects of race have been performed, but in a U.S. 1-year study in patients with type 2 diabetes, the blood glucose-lowering effect was comparable between Caucasians (n=297) and African-Americans (n=33). In a U.S. dose-response study, there was no apparent difference in exposure (AUC) between Caucasians (n=74) and Hispanics (n=33).

Drug-Drug Interactions:

Drug interaction studies performed in healthy volunteers show that PRANDIN had no clinically relevant effect on the pharmacokinetic properties of digoxin, theophylline, or warfarin. Co-administration of cimetidine with PRANDIN did not significantly alter the absorption and disposition of repaglinide.

Additionally, the following drugs were studied in healthy volunteers with co-administration of PRANDIN. Listed below are the results:

Gemfibrozil and Itraconazole: Co-administration of gemfibrozil (600 mg) and a single dose of 0.25 mg PRANDIN (after 3 days of twice-daily 600 mg gemfibrozil) resulted in an 8.1-fold higher repaglinide AUC and prolonged repaglinide half-life from 1.3 to 3.7 hr. Co-administration with itraconazole and a single dose of 0.25 mg PRANDIN (on the third day of a regimen of 200 mg initial dose, twice-daily 100 mg itraconazole) resulted in a 1.4-fold higher repaglinide AUC. Co-administration of both gemfibrozil and itraconazole with PRANDIN resulted in a 19-fold higher repaglinide AUC and prolonged repaglinide half-life to 6.1 hr. Plasma repaglinide concentration at 7 h increased 28.6-fold with gemfibrozil co-administration and 70.4-fold with the gemfibrozil-itraconazole combination (see **PRECAUTIONS, Drug-Drug Interactions).**

Ketoconazole: Co-administration of 200 mg ketoconazole and a single dose of 2 mg PRANDIN (after 4 days of once daily ketoconazole 200 mg) resulted in a 15% and 16% increase in repaglinide AUC and C_{max}, respectively. The increases were from 20.2 ng/mL to 23.5 ng/mL for C_{max} and from 38.9 ng/mL*hr to 44.9 ng/mL*hr for AUC.

Rifampin: Co-administration of 600 mg rifampin and a single dose of 4 mg PRANDIN (after 6 days of once daily rifampin 600 mg) resulted in a 32% and 26% decrease in repaglinide AUC and C_{max}, respectively. The decreases were from 40.4 ng/mL to 29.7 ng/mL for C_{max} and from 56.8 ng/mL*hr to 38.7 ng/mL*hr for AUC.

In another study, co-administration of 600 mg rifam-

pin and a single dose of 4 mg PRANDIN (after 6 days of once daily rifampin 600 mg) resulted in a 48% and 17% decrease in repaglinide median AUC and median C_{max} respectively. The median decreases were from 54 ng/mL*hr to 28 ng/mL*hr for AUC and from 35 ng/mL to 29 ng/mL for C_{max}. PRANDIN administered by itself (after 7 days of once daily rifampin 600 mg) resulted in an 80% and 79% decrease in repaglinide median AUC and C_{max} respectively. The decreases were from 54 ng/mL*hr to 11 ng/mL*hr for AUC and from 35 ng/mL to 7.5 ng/mL for C_{max}.

Levonorgestrel & Ethinyl Estradiol: Co-administration of a combination tablet of 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol administered once daily for 21 days with 2 mg PRANDIN administered three times daily (days 1-4) and a single dose on Day 5 resulted in 20% increases in repaglinide, levonorgestrel, and ethinyl estradiol C_{max}. The increase in repaglinide C_{max} was from 40.5 ng/mL to 47.4 ng/mL. Ethinyl estradiol AUC parameters were increased by 20%, while repaglinide and levonorgestrel AUC values remained unchanged.

Simvastatin: Co-administration of 20 mg simvastatin and a single dose of 2 mg PRANDIN (after 4 days of once daily simvastatin 20 mg and three times daily PRANDIN 2 mg) resulted in a 26% increase in repaglinide C_{max} from 23.6 ng/mL to 29.7 ng/mL. AUC was unchanged.

Nifedipine: Co-administration of 10 mg nifedipine with a single dose of 2 mg PRANDIN (after 4 days of three times daily nifedipine 10 mg and three times daily PRANDIN 2 mg) resulted in unchanged AUC and C_{max} values for both drugs.

Clarithromycin: Co-administration of 250 mg clarith-

romycin and a single dose of 0.25 mg PRANDIN (after 4 days of twice daily clarithromycin 250 mg) resulted in a 40% and 67% increase in repaglinide AUC and C_{max}, respectively. The increase in AUC was from 5.3 ng/mL*hr to 7.5 ng/mL*hr and the increase in C_{max} was from 4.4 ng/mL to 7.3 ng/mL.

Trimethoprim: Co-administration of 160 mg trimethoprim and a single dose of 0.25 mg PRANDIN (after 2 days of twice daily and one dose on the third day of trimethoprim 160 mg) resulted in a 61% and 41% increase in repaglinide AUC and C_{max}, respectively. The increase in AUC was from 5.9 ng/mL*hr to 9.6 ng/mL*hr and the increase in C_{max} was from 4.7 ng/mL to 6.6 ng/mL.

Renal Insufficiency. Single-dose and steady-state pharmacokinetics of repaglinide were compared between patients with type 2 diabetes and normal renal function (CrCl > 80 mL/min), mild to moderate renal function impairment (CrCl = 40 – 80 mL/min), and severe renal function impairment (CrCl= 20 – 40 mL/min). Both AUC and C_{max} of repaglinide were similar in patients with normal and mild to moderately impaired renal function (mean values 56.7 ng/mL*hr vs 57.2 ng/mL*hr and 37.5 ng/mL vs 37.7 ng/mL, respectively.) Patients with severely reduced renal function had elevated mean AUC and C_{max} values (98.0 ng/mL*hr and 50.7 ng/mL, respectively), but this study showed only a weak correlation between repaglinide levels and creatinine clearance. Initial dose adjustment does not appear to be necessary for patients with mild to moderate renal dysfunction. **However, patients with type 2 diabetes who have *severe* renal function impairment should initiate PRANDIN therapy with the 0.5 mg dose – subsequently, patients should be carefully titrated. Studies were not**

conducted in patients with creatinine clearances below 20 mL/min or patients with renal failure requiring hemodialysis.

Hepatic Insufficiency. A single-dose, open-label study was conducted in 12 healthy subjects and 12 patients with chronic liver disease (CLD) classified by Child-Pugh scale and caffeine clearance. Patients with moderate to severe impairment of liver function had higher and more prolonged serum concentrations of both total and unbound repaglinide than healthy subjects ($AUC_{healthy}$: 91.6 ng/mL*hr; $AUC_{CLD\ patients}$: 368.9 ng/mL*hr; $C_{max,\ healthy}$: 46.7 ng/mL; $C_{max,\ CLD\ patients}$: 105.4 ng/mL). AUC was statistically correlated with caffeine clearance. No difference in glucose profiles was observed across patient groups. Patients with impaired liver function may be exposed to higher concentrations of repaglinide and its associated metabolites than would patients with normal liver function receiving usual doses. Therefore, **PRANDIN should be used cautiously in patients with impaired liver function. Longer intervals between dose adjustments should be utilized to allow full assessment of response.**

Clinical Trials

Monotherapy Trials

A four-week, double-blind, placebo-controlled dose-response trial was conducted in 138 patients with type 2 diabetes using doses ranging from 0.25 to 4 mg taken with each of three meals. PRANDIN therapy resulted in dose-proportional glucose lowering over the full dose range. Plasma insulin levels increased after meals and reverted toward baseline before the next meal. Most of the fasting blood glucose-lowering effect was demonstrated within 1-2 weeks.

In a double-blind, placebo-controlled, 3-month dose titration study, PRANDIN or placebo doses for each patient were increased weekly from 0.25 mg through 0.5, 1, and 2 mg, to a maximum of 4 mg, until a fasting plasma glucose (FPG) level <160 mg/dL was achieved or the maximum dose reached. The dose that achieved the targeted control or the maximum dose was continued to end of study. FPG and 2-hour post-prandial glucose (PPG) increased in patients receiving placebo and decreased in patients treated with repaglinide. Differences between the repaglinideand placebo-treated groups were -61 mg/dL (FPG) and -104 mg/dL (PPG). The between-group change in HbA_{1c}, which reflects long-term glycemic control, was 1.7% units.

PRANDIN vs. Placebo Treatment: Mean FPG, PPG, and HbA_{1c} Changes from baseline after 3 months of treatment:

	FPG (mg/dL)		PPG (mg/dL)		HbA_{1c} (%)	
	PL	R	PL	R	PL	R
Baseline	215.3	220.2	245.2	261.7	8.1	8.5
Change from Baseline (at last visit)	30.3	-31.0*	56.5	-47.6*	1.1	-0.6*

FPG = fasting plasma glucose
PPG = post-prandial glucose
PL = placebo (N=33)
R = repaglinide (N=66)
*: $p < 0.05$ for between group difference

Another double-blind, placebo-controlled trial was carried out in 362 patients treated for 24 weeks. The efficacy of 1 and 4 mg preprandial doses was demon-

strated by lowering of fasting blood glucose and by HbA_{1c} at the end of the study. HbA_{1c}, for the PRANDIN- treated groups (1 and 4 mg groups combined) at the end of the study was decreased compared to the placebo-treated group in previously naïve patients and in patients previously treated with oral hypoglycemic agents by 2.1% units and 1.7% units, respectively. In this fixed-dose trial, patients who were naïve to oral hypoglycemic agent therapy and patients in relatively good glycemic control at baseline (HbA_{1c} below 8%) showed greater blood glucose-lowering including a higher frequency of hypoglycemia. Patients who were previously treated and who had baseline $HbA_{1c} \geq 8\%$ reported hypoglycemia at the same rate as patients randomized to placebo. There was no average gain in body weight when patients previously treated with oral hypoglycemic agents were switched to PRANDIN. The average weight gain in patients treated with PRANDIN and not previously treated with sulfonylurea drugs was 3.3%.

The dosing of PRANDIN relative to meal-related insulin release was studied in three trials including 58 patients. Glycemic control was maintained during a period in which the meal and dosing pattern was varied (2, 3 or 4 meals per day; before meals x 2, 3, or 4) compared with a period of 3 regular meals and 3 doses per day (before meals x 3). It was also shown that PRANDIN can be administered at the start of a meal, 15 minutes before, or 30 minutes before the meal with the same blood glucose-lowering effect.

PRANDIN was compared to other insulin secretagogues in 1-year controlled trials to demonstrate comparability of efficacy and safety. Hypoglycemia was reported in 16% of 1228 PRANDIN patients, 20% of 417 glyburide patients, and 19% of 81 glipizide patients.

Of PRANDIN-treated patients with symptomatic hypoglycemia, none developed coma or required hospitalization.

Combination Trials

PRANDIN was studied in combination with metformin in 83 patients not satisfactorily controlled on exercise, diet, and metformin alone. PRANDIN dosage was titrated for 4 to 8 weeks, followed by a 3-month maintenance period. Combination therapy with PRANDIN and metformin resulted in significantly greater improvement in glycemic control as compared to repaglinide or metformin monotherapy. HbA_{1c} was improved by 1% unit and FPG decreased by an additional 35 mg/dL. In this study where metformin dosage was kept constant, the combination therapy of PRANDIN and metformin showed dose-sparing effects with respect to PRANDIN. The greater efficacy response of the combination group was achieved at a lower daily repaglinide dosage than in the PRANDIN monotherapy group (see Table).

PRANDIN and Metformin Therapy: Mean Changes from Baseline in Glycemic Parameters and Weight After 4 to 5 Months of Treatment[1]

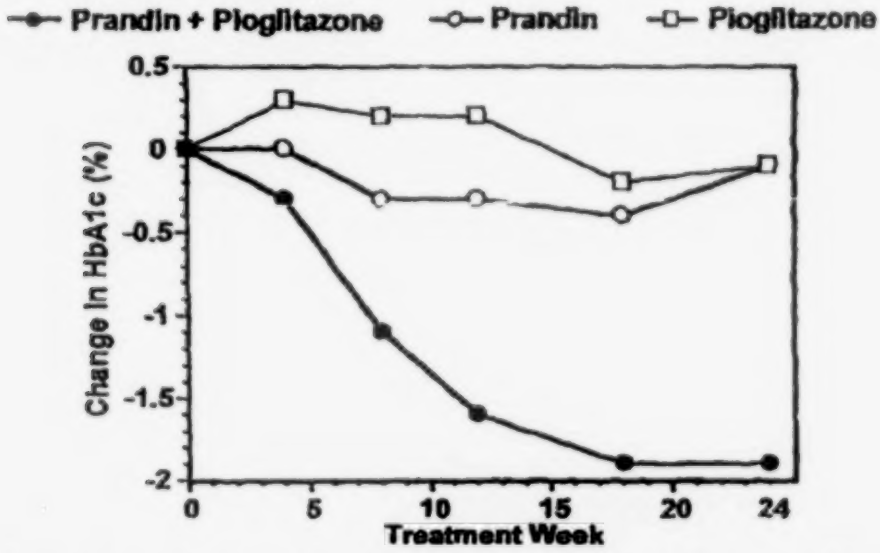
	PRANDIN	Combination	Metformin
N	28	27	27
Median Final Dose (mg/day)	12	6 (PRANDIN) 1500 (metformin)	1500
HbA_{1c} (% units)	-0.38	-1.41*	-0.33
FPG (mg/dL)	8.8	-39.2*	-4.5

Weight (kg)	3.0	2.4 #	-0.90

1: based on intent-to-treat analysis
*: $p < 0.05$, for pairwise comparisons with PRANDIN and metformin.
#: $p < 0.05$, for pairwise comparison with metformin.

A combination therapy regimen of PRANDIN and pioglitazone was compared to monotherapy with either agent alone in a 24-week trial that enrolled 246 patients previously treated with sulfonylurea or metformin monotherapy ($HbA_{1c} > 7.0\%$). Numbers of patients treated were: PRANDIN (N = 61), pioglitazone (N = 62), combination (N = 123). PRANDIN dosage was titrated during the first 12 weeks, followed by a 12-week maintenance period. Combination therapy resulted in significantly greater improvement in glycemic control as compared to monotherapy (figure below). The changes from baseline for completers in FPG (mg/dL) and HbA_{1c} (%), respectively were: -39.8 and -0.1 for PRANDIN, -35.3 and -0.1 for pioglitazone and -92.4 and -1.9 for the combination. In this study where pioglitazone dosage was kept constant, the combination therapy group showed dose-sparing effects with respect to PRANDIN (see figure legend). The greater efficacy response of the combination group was achieved at a lower daily repaglinide dosage than in the PRANDIN monotherapy group. Mean weight increases associated with combination, PRANDIN and pioglitazone therapy were 5.5 kg, 0.3 kg, and 2.0 kg respectively.

HbA_{1c} Values from PRANDIN / Pioglitazone Combination Study



HbA_{1c} values by study week for patients who completed study (combination, N = 101; PRANDIN, N = 35, pioglitazone, N = 26).
Subjects with FPG above 270 mg/dL were withdrawn from the study.
Pioglitazone dose: fixed at 30 mg/day; PRANDIN median final dose: 6 mg/day for combination and 10 mg/day for monotherapy.

A combination therapy regimen of PRANDIN and rosiglitazone was compared to monotherapy with either agent alone in a 24-week trial that enrolled 252 patients previously treated with sulfonylurea or metformin (HbA_{1c} > 7.0%). Combination therapy resulted in significantly greater improvement in glycemic control as compared to monotherapy (table below). The glycemic effects of the combination therapy were dose-sparing with respect to both total daily PRANDIN dosage and total daily rosiglitazone dosage (see table legend). A greater efficacy response of the combination therapy group was achieved with half the median daily

dose of PRANDIN and rosiglitazone, as compared to the respective monotherapy groups. Mean weight change associated with combination therapy was greater than that of PRANDIN monotherapy.

Mean Changes from Baseline in Glycemic Parameters and Weight in a 24-Week PRANDIN/ Rosiglitazone Combination Study[1]

	PRANDIN	Combination	Rosiglitazone
N	63	127	62
HbA_{1c} (%)			
Baseline	9.3	9.1	9.0
Change by 24 weeks	-0.17	-1.43*	-0.56
FPG (mg/dL)			
Baseline	269	257	252
Change by 24 weeks	-54	-94*	-67
Change in Weight (kg)	+1.3	+4.5 #	+3.3

1: based on intent-to-treat analysis
*: p-value $\leq$ 0.001 for comparison to either monotherapy
#: p-value < 0.001 for comparison to PRANDIN
Final median doses: rosiglitazone - 4 mg/day for combination and 8 mg/day for monotherapy;
PRANDIN - 6 mg/day for combination and 12 mg/day for monotherapy

INDICATIONS AND USAGE

PRANDIN is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

CONTRAINDICATIONS

PRANDIN is contraindicated in patients with:

1. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
2. Type 1 diabetes.
3. Known hypersensitivity to the drug or its inactive ingredients.

PRECAUTIONS

General: PRANDIN is not indicated for use in combination with NPH-insulin (See **ADVERSE REACTIONS, Cardiovascular Events)**

Macrovascular Outcomes:

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with PRANDIN or any other anti-diabetic drug.

Hypoglycemia: All oral blood glucose-lowering drugs including repaglinide are capable of producing hypoglycemia. Proper patient selection, dosage, and instructions to the patients are important to avoid hypoglycemic episodes. Hepatic insufficiency may cause elevated repaglinide blood levels and may diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemia. Elderly, debilitated, or malnourished patients, and those with adrenal, pituitary, hepatic, or severe renal insufficiency may be particularly susceptible to the hypoglycemic action of glucose-lowering drugs.

Hypoglycemia may be difficult to recognize in the elderly and in people taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

The frequency of hypoglycemia is greater in patients with type 2 diabetes who have not been previously treated with oral blood glucose-lowering drugs (naïve) or whose HbA_{1c} is less than 8%. PRANDIN should be administered with meals to lessen the risk of hypoglycemia.

Loss of Control of Blood Glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of glycemic control may occur. At such times, it may be necessary to discontinue PRANDIN and administer insulin. The effectiveness of any hypoglycemic drug in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when the drug is first given. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

Information for Patients

Patients should be informed of the potential risks and advantages of PRANDIN and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose and HbA_{1c}. The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development and concomitant administration of other glucose-lowering drugs should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Patients should be instructed to take PRANDIN before meals (2, 3, or 4 times a day preprandially). Doses are usually taken within 15 minutes of the meal but time may vary from immediately preceding the meal to as long as 30 minutes before the meal. **Patients who skip a meal (or add an extra meal) should be instructed to skip (or add) a dose for that meal.**

Laboratory Tests

Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels with a goal of decreasing these levels towards the normal range. During dose adjustment, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Glycosylated hemoglobin may be especially useful for evaluating long-term glycemic control. Postprandial glucose level testing may be clinically helpful in patients whose pre-meal blood glucose levels are satisfactory but whose overall glycemic control (HbA_{1c}) is inadequate.

Drug-Drug Interactions

In vitro data indicate that PRANDIN is metabolized by cytochrome P450 enzymes 2C8 and 3A4. Consequently, repaglinide metabolism may be altered by drugs which influence these cytochrome P450 enzyme systems via induction and inhibition. Caution should therefore be used in patients who are on PRANDIN and taking inhibitors and/or inducers of CYP2C8 and CYP3A4. The effect may be very significant if both enzymes are inhibited at the same time resulting in a substantial increase in repaglinide plasma concentrations. Drugs that are known to inhibit CYP3A4 include antifungal agents like ketoconazole,

itraconazole, and antibacterial agents like erythromycin. Drugs that are known to inhibit CYP2C8 include agents like trimethoprim, gemfibrozil and montelukast. Drugs that induce the CYP3A4 and/or 2C8 enzyme systems include rifampin, barbiturates, and carbamezapine. See **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions.**

In vivo data from a study that evaluated the coadministration of a cytochrome P450 enzyme 3A4 inhibitor, clarithromycin, with PRANDIN resulted in a clinically significant increase in repaglinide plasma levels. In addition, an increase in repaglinide plasma levels was observed in a study that evaluated the coadministration of PRANDIN with trimethoprim, a cytochrome P450 enzyme 2C8 inhibitor . These increases in repaglinide plasma levels may necessitate a PRANDIN dose adjustment. See **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions.**

In vivo data from a study that evaluated the coadministration of gemfibrozil with PRANDIN in healthy subjects resulted in a significant increase in repaglinide blood levels. **Patients taking PRANDIN should not start taking gemfibrozil; patients taking gemfibrozil should not start taking PRANDIN. Concomitant use may result in enhanced and prolonged blood glucose-lowering effects of repaglinide. Caution should be used in patients already on PRANDIN and gemfibrozil - blood glucose levels should be monitored and PRANDIN dose adjustment may be needed. Rare postmarketing events of serious hypoglycemia have been reported in patients taking PRANDIN and gemfibrozil together. Gemfibrozil and itraconazole had a synergistic metabolic inhibitory effect on PRANDIN. Therefore, patients taking PRANDIN and gemfibrozil**

should not take itraconazole. See **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions.**

The hypoglycemic action of oral blood glucose-lowering agents may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving oral blood glucose-lowering agents, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving oral blood glucose-lowering agents, the patient should be observed closely for loss of glycemic control.

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When these drugs are administered to a patient receiving oral blood glucose-lowering agents, the patient should be observed for loss of glycemic control. When these drugs are withdrawn from a patient receiving oral blood glucose-lowering agents, the patient should be observed closely for hypoglycemia.

Carcinogenesis, Mutagenesis, and Impairment Of Fertility

Long-term carcinogenicity studies were performed for 104 weeks at doses up to and including 120 mg/kg body weight/day (rats) and 500 mg/kg body weight/day (mice) or approximately 60 and 125 times clinical exposure, respectively, on a mg/m^2 basis. No evidence of

carcinogenicity was found in mice or female rats. In male rats, there was an increased incidence of benign adenomas of the thyroid and liver. The relevance of these findings to humans is unclear. The no-effect doses for these observations in male rats were 30 mg/kg body weight/day for thyroid tumors and 60 mg/kg body weight/day for liver tumors, which are over 15 and 30 times, respectively, clinical exposure on a mg/m^2 basis.

Repaglinide was non-genotoxic in a battery of *in vivo* and *in vitro* studies: Bacterial mutagenesis (Ames test), *in vitro* forward cell mutation assay in V79 cells (HGPRT), *in vitro* chromosomal aberration assay in human lymphocytes, unscheduled and replicating DNA synthesis in rat liver, and *in vivo* mouse and rat micronucleus tests.

Fertility of male and female rats was unaffected by repaglinide administration at doses up to 80 mg/kg body weight/day (females) and 300 mg/kg body weight/day (males); over 40 times clinical exposure on a mg/m^2 basis.

Pregnancy

Pregnancy category C

Teratogenic Effects: Safety in pregnant women has not been established. Repaglinide was not teratogenic in rats or rabbits at doses 40 times (rats) and approximately 0.8 times (rabbit) clinical exposure (on a mg/m^2 basis) throughout pregnancy. Because animal reproduction studies are not always predictive of human response, PRANDIN should be used during pregnancy only if it is clearly needed.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated

with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Offspring of rat dams exposed to repaglinide at 15 times clinical exposure on a mg/m^2 basis during days 17 to 22 of gestation and during lactation developed nonteratogenic skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. This effect was not seen at doses up to 2.5 times clinical exposure (on a mg/m^2 basis) on days 1 to 22 of pregnancy or at higher doses given during days 1 to 16 of pregnancy. Relevant human exposure has not occurred to date and therefore the safety of PRANDIN administration throughout pregnancy or lactation cannot be established.

Nursing Mothers

In rat reproduction studies, measurable levels of repaglinide were detected in the breast milk of the dams and lowered blood glucose levels were observed in the pups. Cross fostering studies indicated that skeletal changes (see **Nonteratogenic Effects)** could be induced in control pups nursed by treated dams, although this occurred to a lesser degree than those pups treated *in utero.* Although it is not known whether repaglinide is excreted in human milk some oral agents are known to be excreted by this route. Because the potential for hypoglycemia in nursing infants may exist, and because of the effects on nursing animals, a decision should be made as to whether PRANDIN should be discontinued in nursing mothers, or if mothers should discontinue nursing. If PRANDIN is discontinued and if diet alone is inadequate for controlling blood glucose,

insulin therapy should be considered.

Pediatric Use

No studies have been performed in pediatric patients.

Geriatric Use

In repaglinide clinical studies of 24 weeks or greater duration, 415 patients were over 65 years of age. In one-year, active-controlled trials, no differences were seen in effectiveness or adverse events between these subjects and those less than 65 other than the expected age-related increase in cardiovascular events observed for PRANDIN and comparator drugs. There was no increase in frequency or severity of hypoglycemia in older subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals to PRANDIN therapy cannot be ruled out.

ADVERSE REACTIONS

Hypoglycemia: See **PRECAUTIONS and OVERDOSAGE** sections.

PRANDIN has been administered to 2931 individuals during clinical trials. Approximately 1500 of these individuals with type 2 diabetes have been treated for at least 3 months, 1000 for at least 6 months, and 800 for at least 1 year. The majority of these individuals (1228) received PRANDIN in one of five 1-year, active-controlled trials. The comparator drugs in these 1-year trials were oral sulfonylurea drugs (SU) including glyburide and glipizide. Over one year, 13% of PRANDIN patients were discontinued due to adverse events, as were 14% of SU patients. The most common adverse events leading to withdrawal were hyperglycemia, hypoglycemia, and related symptoms (see

PRECAUTIONS). Mild or moderate hypoglycemia occurred in 16% of PRANDIN patients, 20% of glyburide patients, and 19% of glipizide patients.

The table below lists common adverse events for PRANDIN patients compared to both placebo (in trials 12 to 24 weeks duration) and to glyburide and glipizide in one year trials. The adverse event profile of PRANDIN was generally comparable to that for sulfonylurea drugs (SU).

Commonly Reported Adverse Events (% of Patients)*

EVENT	PRANDIN N = 352	PLACEBO N =108	PRANDIN N = 1228	SU N = 498
	Placebo controlled studies		Active controlled studies	
Metabolic				
Hypoglycemia	31**	7	16	20
Respiratory				
URI	16	8	10	10
Sinusitis	6	2	3	4
Rhinitis	3	3	7	8
Bronchitis	2	1	6	7
Gastrointestinal				
Nausea	5	5	3	2
Diarrhea	5	2	4	6
Constipation	3	2	2	3
Vomiting	3	3	2	1
Dyspepsia	2	2	4	2
Musculo-				

skeletal				
Arthralgia	6	3	3	4
Back Pain	5	4	6	7
Other				
Headache	11	10	9	8
Paresthesia	3	3	2	1
Chest pain	3	1	2	1
Urinary tract infection	2	1	3	3
Tooth disorder	2	0	<1	<1
Allergy	2	0	1	<1

*: Events ≥2% for the PRANDIN group in the placebo-controlled studies and ≥ events in the placebo group

: See trial description in **CLINICAL PHARMACOLOGY, Clinical Trials

Cardiovascular Events

In one-year trials comparing PRANDIN to sulfonylurea drugs, the incidence of angina was comparable (1.8%) for both treatments, with an incidence of chest pain of 1.8% for PRANDIN and 1.0% for sulfonylureas. The incidence of other selected cardiovascular events (hypertension, abnormal EKG, myocardial infarction, arrhythmias, and palpitations) was ≤ 1% and not different between PRANDIN and the comparator drugs.

The incidence of total serious cardiovascular adverse events, including ischemia, was higher for repaglinide (4%) than for sulfonylurea drugs (3%) in controlled comparator clinical trials. In 1-year controlled trials, PRANDIN treatment was not associated with excess mortality when compared to the rates observed with other oral hypoglycemic agent therapies.

Summary of Serious Cardiovascular Events (% of total patients with events) in Trials Comparing PRANDIN to Sulfonylureas

	PRANDIN	SU*
Total Exposed	1228	498
Serious CV Events	4%	3%
Cardiac Ischemic Events	2%	2%
Deaths due to CV Events	0.5%	0.4%

*: glyburide and glipizide

Seven controlled clinical trials included PRANDIN combination therapy with NPH-insulin (n=431), insulin formulations alone (n=388) or other combinations (sulfonylurea plus NPH-insulin or PRANDIN plus metformin) (n=120). There were six serious adverse events of myocardial ischemia in patients treated with PRANDIN plus NPH-insulin from two studies, and one event in patients using insulin formulations alone from another study.

Infrequent Adverse Events (<1% of Patients)

Less common adverse clinical or laboratory events observed in clinical trials included elevated liver enzymes, thrombocytopenia, leukopenia, and anaphylactoid reactions.

Although no causal relationship with repaglinide has been established, postmarketing experience includes reports of the following rare adverse events: alopecia, hemolytic anemia, pancreatitis, Stevens-Johnson Syndrome, and severe hepatic dysfunction including jaundice and hepatitis.

Combination Therapy with Thiazolidinediones

During 24-week treatment clinical trials of PRANDIN-rosiglitazone or PRANDIN-pioglitazone combination therapy (a total of 250 patients in combination therapy), hypoglycemia (blood glucose < 50 mg/dL) occurred in 7% of combination therapy patients in comparison to 7% for PRANDIN monotherapy, and 2% for thiazolidinedione monotherapy.

Peripheral edema was reported in 12 out of 250 PRANDIN-thiazolidinedione combination therapy patients and 3 out of 124 thiazolidinedione monotherapy patients, with no cases reported in these trials for PRANDIN monotherapy. When corrected for dropout rates of the treatment groups, the percentage of patients having events of peripheral edema per 24 weeks of treatment were 5% for PRANDIN-thiazolidinedione combination therapy, and 4% for thiazolidinedione monotherapy. There were reports in 2 of 250 patients (0.8%) treated with PRANDINthiazolidinedione therapy of episodes of edema with congestive heart failure. Both patients had a prior history of coronary artery disease and recovered after treatment with diuretic agents. No comparable cases in the monotherapy treatment groups were reported.

Mean change in weight from baseline was +4.9 kg for PRANDIN-thiazolidinedione therapy. There were no patients on PRANDIN-thiazolidinedione combination therapy who had elevations of liver transaminases (defined as 3 times the upper limit of normal levels).

OVERDOSAGE

In a clinical trial, patients received increasing doses of PRANDIN up to 80 mg a day for 14 days. There were few adverse effects other than those associated with the intended effect of lowering blood glucose. Hypoglyce-

mia did not occur when meals were given with these high doses. Hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring may continue until the physician is assured that the patient is out of danger. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery. There is no evidence that repaglinide is dialyzable using hemodialysis.

Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of type 2 diabetes with PRANDIN.

The patient's blood glucose should be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e., loss of an adequate blood glucose-lowering response after an initial period of effectiveness.

Glycosylated hemoglobin levels are of value in monitoring the patient's longer term response to therapy.

Short-term administration of PRANDIN may be sufficient during periods of transient loss of control in patients usually well controlled on diet.

PRANDIN doses are usually taken within 15 minutes of the meal but time may vary from immediately preceding the meal to as long as 30 minutes before the meal.

Starting Dose

For patients not previously treated or whose HbA_{1c} is < 8%, the starting dose should be 0.5 mg with each meal. For patients previously treated with blood glucose-lowering drugs and whose HbA_{1c} is ≥ 8%, the initial dose is 1 or 2 mg with each meal preprandially (see previous paragraph).

Dose Adjustment

Dosing adjustments should be determined by blood glucose response, usually fasting blood glucose. Postprandial glucose levels testing may be clinically helpful in patients whose pre-meal blood glucose levels are satisfactory but whose overall glycemic control (HbA_{1c}) is inadequate. The preprandial dose should be doubled up to 4 mg with each meal until satisfactory blood glucose response is achieved. At least one week should elapse to assess response after each dose adjustment.

The recommended dose range is 0.5 mg to 4 mg taken with meals. PRANDIN may be dosed preprandially 2, 3, or 4 times a day in response to changes in the patient's meal pattern. The maximum recommended daily dose is 16 mg.

Patient Management

Long-term efficacy should be monitored by measurement of HbA_{1c} levels approximately every 3 months. Failure to follow an appropriate dosage regimen may

precipitate hypoglycemia or hyperglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy including hypoglycemia. When hypoglycemia occurs in patients taking a combination of PRANDIN and a thiazolidinedione or PRANDIN and metformin, the dose of PRANDIN should be reduced.

Patients Receiving Other Oral Hypoglycemic Agents

When PRANDIN is used to replace therapy with other oral hypoglycemic agents, PRANDIN may be started on the day after the final dose is given. Patients should then be observed carefully for hypoglycemia due to potential overlapping of drug effects. When transferred from longer half-life sulfonylurea agents (e.g., chlorpropamide) to repaglinide, close monitoring may be indicated for up to one week or longer.

Combination Therapy

If PRANDIN monotherapy does not result in adequate glycemic control, metformin or a thiazolidinedione may be added. If metformin or thiazolidinedione monotherapy does not provide adequate control, PRANDIN may be added. The starting dose and dose adjustments for PRANDIN combination therapy is the same as for PRANDIN monotherapy. The dose of each drug should be carefully adjusted to determine the minimal dose required to achieve the desired pharmacologic effect. Failure to do so could result in an increase in the incidence of hypoglycemic episodes. Appropriate monitoring of FPG and HbA_{1c} measurements should be used to ensure that the patient is not subjected to excessive drug exposure or increased probability of secondary drug failure.

HOW SUPPLIED

PRANDIN (repaglinide) tablets are supplied as unscored, biconvex tablets available in 0.5 mg (white), 1 mg (yellow) and 2 mg (peach) strengths. Tablets are embossed with the Novo Nordisk (Apis) bull symbol and colored to indicate strength.

0.5 mg tablets (white)	Bottles of 100	NDC 00169-0081-81
	Bottles of 500	NDC 00169-0081-82
	Bottles of 1000	NDC 00169-0081-83
1 mg tablets (yellow)	Bottles of 100	NDC 00169-0082-81
	Bottles of 500	NDC 00169-0082-82
	Bottles of 1000	NDC 00169-0082-83
2 mg tablets (peach)	Bottles of 100	NDC 00169-0084-81
	Bottles of 500	NDC 00169-0084-82
	Bottles of 1000	NDC 00169-0084-83

Do not store above 25° C (77° F).

Protect from moisture. Keep bottles tightly closed. Dispense in tight containers with safety closures.

Licensed Under US Patent No. RE 37,035.

PRANDIN® is a registered trademark of Novo Nordisk A/S.

Manufactured in Germany for
Novo Nordisk Inc.
Princeton, NJ 08540
1-800-727-6500

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Date of Issue:
Version:

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[Electronic Signature Page Omitted]

WINSTON & STRAWN LLP

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jhurst@winston.com 0737 8 JUL 14 P4:40

July 14, 2008

VIA HAND DELIVERY
Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services,
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Re: ANDAs for Repaglinide Containing "Section viii" Statements for U.S. Patent No. 6,677,358

Dear Sir or Madam:

CITIZEN PETITION

We file this petition on behalf of Caraco Pharmaceutical Laboratories, Ltd., with respect to Caraco's ANDA for repaglinide, No. 77-571. Caraco filed that ANDA on February 9, 2005, and FDA tentatively approved it on August 10, 2007.

The reference listed drug for Caraco's ANDA is Novo Nordisk's product sold under the brand name Prandin. Novo Nordisk has two patents listed in the Orange Book relating to Prandin: U.S. Patent Nos. 6,677,358 ("the '358 patent") and RE37035 ("the '035 patent"). Those patents are set to expire on June 12, 2018 and March 14, 2009, respectively. The Orange Book also lists a patent use code of U-546 for the '358 patent, which is defined as the use of repaglinide in combination with metformin to lower blood glucose.

Caraco certified under section 505(j)(2)(A)(vii)(III) of Federal Food, Drug, and Cosmetic Act ("the Act") that it will not market repaglinide prior to the expiration of the '035 patent.

For the '358 patent, Caraco initially certified under section 505(j)(2)(A)(vii)(IV) of the Act ("paragraph IV certification") that the '358 patent is invalid, unenforceable, or will not be infringed by Caraco's ANDA product. The '358 patent contains three composition claims (claims 1-3), one product claim (claim 5), and one method of use claim (claim 4). Caraco does not intend to market generic repaglinide for the method of use covered in claim 4. Accordingly, on April 2, 2004, and based upon FDA's letter to Caraco dated March 17, 2008, suggesting that Caraco "split the patent certification," Caraco amended its ANDA to include a statement under section 505(j)(2)(A)(viii) of the Act ("section viii statement") as to the method of use claim in the '358 patent (claim 4). The section viii statement certifies that Caraco does not seek approval for the method of use covered in claim 4.

A. Action Requested: Require Any Repaglinide ANDAs Containing Only A Section viii Statement For The '358 Patent To Convert To A Paragraph IV Certification Or A Split-Certification.

The FDA does not publicly disclose whether a party has filed an ANDA that does not include a Paragraph IV certification. It thus is possible that a party has filed, or will file, an ANDA for repaglinide with a section viii statement for the entire '358 patent that does not also contain a paragraph IV certification. Caraco requests that if such a filing has occurred, or does occur, that the FDA require the applicant to

convert to a paragraph IV certification with regard to, at a minimum, claims 1, 2, 3, and 5. This is the correct course of action because section viii statements can only be made for method of use claims; they cannot be made for the composition and product claims in the '358 patent.

Caraco's request does not extend to claim 4 of the '358 patent, which is directed to a method of use. For claim 4, Caraco believes it is appropriate for a party to file either: (a) a paragraph IV certification, if the party is seeking approval for that method of use; or (b) a split-certification that includes a section viii statement, if the party is not seeking approval for that method of use and has "carved out" the appropriate language for the patented method of use from its proposed labeling.

In other words, Caraco requests confirmation that the FDA will require any ANDA as to repaglinide that includes a section viii statement as to the '358 patent to also include a paragraph IV certification to address claims 1, 2, 3, and 5. The FDA should approve no ANDA as to repaglinide based solely on a section viii statement with regard to the '358 patent because that statement can only address claim 4.

B. Statement of Grounds

1. Section viii Statements Are Only Applicable For Method Of Use Patent Claims.

Both the Act and the regulations that FDA has promulgated to implement the Act provide that a section viii statement is applicable only for patent claims describing a method of use. The Act mandates that an ANDA shall contain:

> if with respect to the listed drug . . . information was filed . . . *for a method of use patent* which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

21 U.S.C. § 355(j)(2)(A)(viii) (emphasis added).

The implementing regulations – entitled "Method Of Use Patent" – similarly limit section viii statements to patent claims covering a method of use:

> If patent information is submitted under section 505(b) or (c) of the act and § 314.53 *for a patent claiming a method of using the listed drug*, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, a statement explaining that the method of use patent does not claim any of the proposed indications.

21 C.F.R. § 314.94(a)(12)(iii) (emphasis added).

Both the statute and the regulation clearly indicate that a section viii statement is only appropriate with respect to method of use patent claims. For all other types of claims, including composition and product claims, the ANDA filer must instead certify to the patent under Section 505(j)(2)(A)(vii).

2. Novo Nordisk's '358 Patent Contains Claims That Are Not Method Of Use Claims.

As discussed above, the '358 patent contains five claims, of which only the fourth is a method of use claim. These claims cover: (1) the pharmaceutical composition of repaglinide and metformin together

with a suitable carrier; (2) the same composition as a tablet; (3) the same composition as a capsule; (4) a method for treating non-insulin dependent diabetes mellitus (NIDDM) with a combination of repaglinide and metformin (associated with use code U-546); and (5) a kit for the treatment of NIDDM consisting of a formulation of repaglinide and metformin.

Most of the claims in the '358 patent are not for a method of use: claims 1-3 are for pharmaceutical compositions, and claim 5 is a product claim (it claims a "kit" consisting of doses of repaglinide and metformin). The statute and regulation quoted above both explicitly state that a section viii statement can only be made for patent claims covering a method of use. As a result, a section viii statement by an ANDA filer would be inappropriate for claims 1, 2, 3, and 5 of the '358 patent.

3. Why Is Caraco Concerned?

Caraco is the first party to file an ANDA for repaglinide containing a paragraph IV certification to the '358 patent. As a result, Caraco expects to be eligible for the 180-day exclusivity period as defined in 21 C.F.R. § 314.107(c)(1). By the terms of that regulation, however, such exclusivity is only with respect to other ANDAs that also contain paragraph IV certifications.

If another party were permitted to file an ANDA with a section viii statement as to the entire '358 patent, despite the fact that such an application would be inappropriate for the claims of the '358 patent that are not method of use claims, such a party could be able to market repaglinide before or during Caraco's exclusivity period. This result would drastically re-

duce the benefit of the exclusivity period to Caraco and frustrate the incentive structure of the Act.

Again, Caraco is not aware of any party that has already filed an ANDA for repaglinide with a section viii statement for the '358 patent. Rather, Caraco files this petition out of an abundance of caution to secure confirmation from the FDA that Caraco's marketing exclusively under the Act will not be frustrated by improper use of the section viii statement procedure.

C. Environmental Impact

The actions requested by this Petition are subject to categorical exclusion pursuant to 21 C.F.R. § 25.30.

D. Economic Impact

An Economic Impact Statement will be provided at the request of the Commissioner.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Sincerely,

/s/ James F. Hurst/CBK
James F. Hurst

cc: Charles B. Klein
David S. Bloch, M.P.H.

CBK:jm

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

DEC 4 2008

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Re: Docket Nos. FDA-2008-P-0343 and FDA-2008-P-0411

Dear Ms. Wilk-Orescan and Mr. Hurst:

This letter responds to the citizen petition submitted to the Food and Drug Administration (FDA or the Agency) by Novo Nordisk Inc. (Novo Nordisk) on June 9, 2008, and a supplement submitted on July 21, 2008 (Novo Nordisk Petition or Petition). The petition requests that FDA refrain from approving any abbreviated new drug application (ANDA) for a repaglinide product that omits information on metformin combination therapy, which is protected by patent and currently appears in the labeling of the innovator product, Prandin (repaglinide). The Petition contends that the omission of the metformin combination therapy information would render generic versions of Prandin less safe and effective for the remaining, nonprotected conditions of use.

We have carefully reviewed the arguments in the Novo Nordisk Petition. For the reasons stated below, we deny your request.

We are also responding to a related citizen petition submitted to FDA by Winston and Strawn LLP on behalf of Caraco Pharmaceuticals Laboratories, Ltd. (Caraco), on July 14, 2008 (Caraco Petition). The Caraco Petition requests that FDA require any ANDAs for repaglinide that include only a section viii statement for the method-of-use claim of the U.S. Pat. No. 6,677,358 (the '358 patent) for combination therapy with metformin also include a paragraph IV certification to address the other claims of the '358 patent.

We have carefully reviewed the Caraco Petition, and for the reasons below, we grant your request

I. BACKGROUND

A. Prandin

On December 22, 1997, FDA approved the new drug application (NDA) held by Novo Nordisk for Prandin (repaglinide) (NDA 20-741). Prandin is currently indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (non-insulin mellitus). At the time of initial approval, Prandin's indication was described as a monotherapy treatment and for use in combination with metformin. On October 21, 2002, FDA approved a supplement to this NDA that provided for the use of Prandin in combination with thiazolidinediones (TZDs).[1]

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[1] The INDICATIONS AND USAGE section for the Prandin labeling prior to July 2008 was as follows:

> PRANDIN is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with type 2

In early 2008, FDA reevaluated the labeling for all oral antidiabetic drugs and requested that all oral antidiabetic agents have the following simplified indication: "Drug X is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus." Pertinent efficacy and safety information from the various clinical trials would still be described in appropriate sections of the label (e.g., CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, Clinical Trials).

In response to this FDA request that all oral antidiabetic drug products have a simplified indication, Novo Nordisk submitted a supplement to the Agency requesting that the Prandin labeling be changed to comply with this directive. Effective July 14, 2008, the labeling for Prandin was revised to exclude specific information in the INDICATIONS AND USAGE section regarding the combination therapy use of this drug product with metformin and TZDs. The newly revised INDICATIONS AND USAGE section reads as follows:

> PRANDIN is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

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diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled satisfactorily by diet and exercise alone.

PRANDIN is also indicated for combination therapy use (with metformin or thiazolidinediones) to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise plus monotherapy with any of the following agents: metformin, sulfonylureas, repaglinide, or thiazolidinediones....

The data supporting repaglinide monotherapy and combination therapy with metformin or a TZD are derived from separate clinical trials and are described separately in the Prandin labeling.

FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) lists two patents for Prandin: U.S. Pat No. 37,035 (the '035 patent) and the '358 patent. The '035 patent expires on March 14, 2009, and claims, among other things, the chemical composition of repaglinide. The '358 patent expires on June 12, 2018, and claims, among other things, the use of repaglinide in combination with metformin. Specifically, according to the Novo Nordisk Petition, the '358 patent contains 5 claims: claims 1-3 deal with a pharmaceutical composition containing both repaglinide and metformin; claim 5 concerns a kit comprised of at least repaglinide and metformin; and claim 4, the focus of these petitions, concerns the method of use for the combination of repaglinide and metformin in treating type 2 diabetes (Petition at 3).

B. ANDA for Repaglinide

As explained in the Caraco Petition, Caraco submitted ANDA 77-751 to FDA for repaglinide tablets (0.5 milligram (mg), 1 mg, and 2 mg). The ANDA initially contained a paragraph III certification with respect to the '035 patent and a paragraph IV certification as to the method-of-use claim in the '358 patent. Caraco amended its ANDA in April 2008 to also include a section viii statement (method-of-use statement) to the '358 patent. The section viii statement declares that Caraco is not seeking approval for the method of use claimed by the '358 patent (i.e., that it is not

seeking the approval for the method of use for the repaglinide/metformin combination therapy).

C. The Statutory and Regulatory Basis for Patent Protection for NDAs and for Labeling Differences for ANDAs

The Federal Food, Drug and Cosmetic Act (the Act) and FDA regulations require that a sponsor seeking to market an innovator drug submit an NDA. NDAs contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug for the indication for which approval is sought. The Act and FDA regulations also require that a sponsor of an NDA submit to FDA a list of patents claiming the approved drug substance or drug product, or claiming an approved method of using the drug product described in the NDA. Specifically, section 505(b)(1) of the Act (21 U.S.C. 355(b)(1)) requires NDA applicants to file as part of the NDA "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or *which claims a method of using such drug* and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug" (emphasis added).[2] FDA is required to publish patent information for drugs approved under section 505(c) and does so in the Orange Book (section 505(b)(1), (c)(2), and (j)(7) of the Act and 21 CFR 314.53(e)).

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[2] Section 505(c)(2) of the Act imposes an additional patent submission requirement on holders of approved NDAs when those holders subsequently obtain new patent information that could not have been submitted with the NDA.

A drug product with an effective approval under section 505(c) of the Act is known as a *listed drug*.[3] Under provisions added to the Act by the 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments), Public Law No. 98-417, 98 Stat. 1585, the Act permits submission of ANDAs for approval of generic versions of listed drugs (see section 505(j) of the Act). The ANDA process shortens the time and effort needed for approval by, among other things, allowing an ANDA applicant to rely on FDA's previous finding of safety and effectiveness for a listed drug rather than requiring the ANDA applicant to independently demonstrate the safety and effectiveness of its proposed drug. To rely on such a finding, the ANDA applicant must show that its proposed drug product is the same as the listed drug in many respects (including active ingredient, dosage form, strength, route of administration, and, with certain narrow exceptions, labeling), and that its product is bioequivalent to the listed drug.

Each ANDA applicant must identify the listed drug on which it seeks to rely for approval. As described in more detail below, the timing of ANDA approval depends on, among other things, the intellectual property protections for the listed drug the ANDA refer-

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[3] Under 21 CFR 314.3(b), "*[l]isted drug* means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness." A listed drug is identified as having an effective approval in the Orange Book, which includes patent information for each approved drug (§ 314.53(e)).

ences and whether the ANDA applicant challenges those protections (see section 505(b), (c), (j)(2)(A)(vii), and (j)(5)(B) of the Act).[4] In general, an ANDA may not obtain final approval until listed patents and marketing exclusivity have expired or until NDA holders and patent owners have had the opportunity to defend relevant patent rights in court.

Specifically, with respect to each patent submitted by the sponsor for the listed drug and listed in the Orange Book, the ANDA applicant generally must submit to FDA one of four specified certifications under section 505(j)(2)(A)(vii) of the Act. The certification must state one of the following:

> (I) That the required patent information relating to such patent has not been filed (paragraph I certification)
>
> (II) That such patent has expired (paragraph II certification)
>
> (III) That the patent will expire on a particular date (paragraph III certification)
>
> (IV) That such patent is invalid or will not be infringed by the drug for which approval is being sought (paragraph IV certification)

The purpose of these certifications is "to give notice, if necessary, to the patent holder so that any legal disputes regarding the scope of the patent and the pos-

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[4] Relevant intellectual property protections affecting the timing of ANDA approval include marketing exclusivity and listed patent protection for the listed drug. Marketing exclusivity is not at issue here, so this response does not address the effect of exclusivity on ANDA approval but focuses, instead, on relevant patent protection.

sibility of infringement can be resolved as quickly as possible" *(Torpharm, Inc.* v. *Thompson*, 260 F. Supp. 2d 69, 71 (D.D.C. 2003)).

If an applicant files a paragraph I or II certification, the patent in question will not delay ANDA approval. If an applicant files a paragraph III certification, the applicant agrees to wait until the relevant patent has expired before seeking full effective approval of its ANDA.

If, however, an applicant wishes to seek approval of its ANDA before a listed patent has expired by challenging the validity of a patent or claiming that a patent would not be infringed by the product proposed in the ANDA, the applicant must submit a paragraph IV certification to FDA. The applicant filing a paragraph IV certification must also provide a notice to the NDA holder and the patent owner stating that the application has been submitted and explaining the factual and legal bases for the applicant's opinion that the patent is invalid or not infringed (see section 505(b)(2)(B) and (j)(2)(B) of the Act).

The filing of a paragraph IV certification "for a drug claimed in a patent or the use of which is claimed in a patent" is an act of patent infringement (35 U.S.C. 271(c)(2)(A)). If the patent owner or NDA holder brings a patent infringement suit against the ANDA applicant within 45 days of the date it received notice of the paragraph IV certification, the approval of the ANDA will be stayed for 30 months from the date of such receipt by the patent owner and NDA holder, unless a court decision is reached earlier in the patent case or the patent court otherwise orders a longer or shorter period (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the Act). When the 30 months have ex-

pired, the patent ceases to be a barrier to final ANDA approval, even if the patent litigation is ongoing. Similarly, if the NDA holder and patent owner receive notice of a paragraph IV certification and decline to sue within 45 days of receipt of notice, the patent will not be a barrier to ANDA approval.

These paragraph I, II, III, and IV certifications are not the only manner in which an ANDA applicant may address all relevant patents. When a patent is listed only for a method of use, an ANDA applicant seeking to omit that approved method of use covered by the listed patent need not file a paragraph I to IV certification for that patent. Instead, the applicant may submit a *section viii statement* acknowledging that a given method-of-use patent has been listed, but stating that the patent at issue does not claim a use for which the applicant seeks approval (see section 505(j)(2)(A)(viii) of the Act). Specifically, section 505(j)(2)(A)(viii) of the Act provides that "if with respect to the listed drug referred to in [section 505(j)(2)(A)(i)] information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, [the ANDA must contain] a statement that the method of use patent does not claim such a use." Such a statement requires the ANDA applicant to omit from its labeling information pertaining to the protected use (21 CFR 314.92(a)(1) and 314.94(a)(12)(iii)). If an ANDA applicant files a section viii statement, the patent claiming the protected method of use will not serve as a barrier to ANDA approval.[5]

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[5] See also H.R. Rep. No. 857 (Part 1), 98th Cong., 2d sess. 21.

FDA implementing regulations at § 314.94(a)(12)(iii) describe the applicability of the section viii statement. Section 314.94(a)(12)(iii) states:

> If patent information is submitted under section 505(b) or (c) of the [A]ct and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, [the ANDA applicant must submit] a statement explaining that the method of use patent does not claim any of the proposed indications.[6]

> ...The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved. For example, if the listed drug has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval for only the angina pectoris indication.

[6] FDA regulations implementing this statutory provision use the term *indications* to refer to information an ANDA applicant omits from its labeling in the context of submitting a statement that a protected use of a drug is not claimed in a listed patent (§ 314.94(a)(12)(iii)). However, the preambles for the proposed rule and final rule on patent and exclusivity provisions related to ANDA approval express no intent to distinguish between method of use and indication, using the terms interchangeably (see, e.g., 59 FR 50338 at 50347 (October 3, 1994)). Moreover, the preamble to the final rule emphasizes that an ANDA applicant does not have the option of choosing between a paragraph IV certification and a section viii statement where the patent claims only a method of use; where the labeling does not include the indication, only the section viii statement is appropriate (id.). The preamble to the proposed rule states that where "the labeling for the applicant's proposed drug product does not include any indications that are covered by the use patent," the ANDA applicant would submit a section viii statement rather

Accordingly, FDA regulations also expressly recognize that by submitting a section viii statement, an ANDA applicant may omit from the proposed labeling a method of use protected by a listed patent, and therefore need not seek approval for that use.[7]

The right to file a section viii statement and carve out from labeling method-of-use information protected by a patent has been upheld by the courts. Thus, in *Purepac Pharmaceutical Company* v. *Thompson*, 354 F.3d 877 (D.C. Cir. 2004), the D.C. Circuit stated that a "section viii statement indicates that a patent poses no bar to approval of an ANDA because the applicant seeks to market the drug for a use other than the one encompassed by the patent" (id. at 880). Similarly, in *Torpharm*, 260 F. Supp. 2d at 73, the D.C. District Court stated that a section viii statement "avers that the patent in question has been listed, but does not claim a use for which the applicant seeks FDA approval." These courts have upheld the Agency's interpretation that an ANDA applicant may choose not to

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than a paragraph IV certification (54 FR 28872 at 28886 (July 10, 1989)).

[7] See also the final rule, Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed (68 FR 36676 (June 18, 2003)). In the preamble to this final rule, we stated that the section viii statement permits an ANDA applicant to "avoid certifying to a patent by stating that it is not seeking approval for the use claimed in the listed patent" (68 FR 36676 at 36682). We stated, "[o]ur position has been that, for an ANDA applicant to file a section viii statement, it must 'carve-out' from the proposed ANDA labeling, the labeling protected by the listed patent" (id.).

seek approval for a method of use protected by a listed patent, and under those circumstances, that patent will not be a barrier to ANDA approval.

Thus, under the procedures established in the Hatch-Waxman Amendments, an ANDA will not be approved until all listed patents (1) have expired, (2) have been successfully challenged, (3) have been subject to a paragraph IV certification pursuant to which the patent owner or NDA holder has declined to sue within 45 days, (4) have been subject to a paragraph IV certification that led to a lawsuit and either a decision favorable to the ANDA applicant or a 30-month stay that has since expired, or (5) are subject to a section viii statement and a corresponding labeling carve-out.

D. Requirements Regarding ANDA Labeling

Section 505(j)(2)(A)(i) of the Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." This language reflects Congress's intent that the generic drug be safe and effective for each "condition of use" prescribed, recommended, or suggested in the generic drug labeling. However, it does not require that an ANDA be approved for each condition of use for which the reference listed drug is approved. Thus, in § 314.92(a)(1), FDA has explicitly stated that a proposed generic drug product must have the same conditions of use as the listed drug, "except that conditions of use for which approval cannot be granted because of . . . an existing *patent* may be omitted" (emphasis added).

The Act also requires that an ANDA contain "information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug. . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the Act] or because the new drug and the listed drug are produced or distributed by different manufacturers" (section 505(j)(2)(A)(v) of the Act). A parallel provision appears in section 505(j)(4)(G) of the Act.[8]

Similarly, the regulations at § 314.94(a)(8)(iv) require the following:

> Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the [generic] drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 [21 CFR 314.93] or because the drug product and the reference listed drug are produced or distributed by different manufacturers.

Section 314.94(a)(8)(iv) sets forth examples of permissible differences in labeling that may result because the generic drug product and reference listed

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[8] Section 505(j)(4)(G) of the Act provides that FDA must approve an ANDA unless, among other things, the "information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for [the reference listed drug] except for changes required because of differences approved under [an ANDA suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers."

drug are produced or distributed by different manufacturers. These differences include the following:

> . . . differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or *omission of an indication or other aspect of labeling protected by patent* [emphasis added] or accorded exclusivity under section 505(j)(4)(D) of the [A]ct.[9]

The regulations at 21 CFR 314.127(a)(7) further provide that to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are *protected by patent* [emphasis added]," we must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining nonprotected conditions of use."

Relevant case law affirms an ANDA applicant's ability to carve out protected labeling without violating the "same labeling" requirement. For example, in *Bristol-Myers Squibb* v. *Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996), the D.C. Circuit ruled that "the statute expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label; whether the label for the new generic lists every indication approved for the use of the pioneer is a matter of indifference." Similarly, in *Sigma-Tau Pharmaceuticals, Inc. v Schwetz*, 288 F.3d 141, 148, fn. 3 (4th Cir. 2002), the Fourth Circuit

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[9] We note that, due to a series of amendments to the Act, the reference in § 314.94(a)(8)(iv) to section 505(j)(4)(D) of the Act corresponds to current section 505(j)(5)(F) of the Act.

upheld the right of an ANDA applicant to carve out an indication protected by orphan drug exclusivity as a permissible difference due to difference in manufacturer. Thus, under the statute, regulations, and applicable case law, the carve-out of patent-protected labeling is generally permitted as a permissible difference due to difference in manufacturer if the omission does not render the proposed drug product less safe or effective for the conditions of use that remain in the labeling.

II. ANALYSIS OF THE NOVO NORDISK PETITION

In your Petition, you state that at least one ANDA applicant, Caraco, has received tentative approval for a generic version of repaglinide (Petition at 2). You state that Caraco's proposed labeling for a generic repaglinide omits the information regarding metformin combination therapy. You argue that labeling omitting the metformin combination therapy information would result in insufficient and misleading information to physicians prescribing the drug product, the pharmacists dispensing the drug, and patients using the drug (Petition at 2).

On a number of occasions, we have affirmed our authority to approve generic drug products with carved-out labeling. For example, in our response to the citizen petition concerning ANDAs for ribavirin,[10] we affirmed our authority to approve generic ribavirin drug products with labeling that omits protected information and rejected arguments similar to the ones

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[10] April 6, 2004, letter from Steven K. Galson, Acting Director, Center for Drug Evaluation and Research, to David M. Fox, Docket No. 2003P-0321/CP1 (Ribavirin Response Letter).

you raise here. We reiterated this position recently in our response to a citizen petition concerning ANDAs for amifostine with a protected indication carved out;[11] in our response to a citizen petition concerning ANDAs for dronabinol;[12] and in our response to a citizen petition concerning ANDAs for ramipril.[13] In addition, in our response to a citizen petition concerning irinotecan,[14] we rejected the petitioner's arguments regarding carved-out labeling for that drug product when used in combination with another drug product, stating that we would allow ANDAs for irinotecan to omit from their labeling information on the use of the drug in combination with 5-fluorouracil and leucovorin because such omission did not render the drug less safe or effective for the remaining non-protected conditions of use.

A. A Section viii Statement Is Appropriate for the '358 Patent.

You state that a section viii statement, with respect to the '358 patent, is inappropriate because the ANDA applicant is seeking approval to market the drug

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[11] March 13, 2008, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to William C. Bertrand, Jr., Docket No. 2006P-0410/CP1 (Amifostine Response Letter).

[12] April 25, 2008, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Victor Raczkowski, M.D., Docket No. FDA-2007-P-0169 (Dronabinol Response Letter).

[13] June 18, 2008, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Thomas K. Rogers, Docket No. FDA-2008-P-0304 (Ramipril Response Letter).

[14] July 28, 2008. letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Ernest Lengle, Ph.D., Docket No. FDA-2008-P-0069 (Irinotecan Response Letter).

product for a limited subset of all uses for which the reference drug has been approved (Petition at 5). You claim that in accordance with an FDA directive for all oral antidiabetic drugs, the proposed revised labeling for Prandin will only contain a single indication for Prandin. You also claim that because the Prandin labeling has only one indication, there is no additional indication or use that can be carved out by a section viii statement (Petition at 6). We disagree that a section viii statement, with respect to the '358 patent, is inappropriate.

As explained in section I.A, the Prandin labeling currently contains only 1 indication: as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. We disagree, however, with your conclusions that a section viii statement is inappropriate because there is not a separate combination indication to carve out or because use in combination with metformin was approved at the time of the initial NDA approval. The statute and regulations do not require a separate indication for a carve-out. Section 505(j)(2)(A)(viii) of the Act refers to "a use" for which the applicant is seeking approval.

Although the regulations refer to the term indication, FDA has expressed no intent to distinguish between method of use and indications (see footnote 6). In fact, FDA has permitted the carve-out of methods of use that are not a separate indication in several of the examples cited in your Petition (see, e.g., tramadol, oxandrolone). Specifically, in tramadol, we concluded that we need not resolve the issue of whether tramadol is approved for only a single indication (the treatment of moderate to moderately severe pain) or is separately indicated for chronic and acute pain where portions of tramadol's labeling relating to a 50

mg, 16-day titrating regimen are not protected by patent and the requirements of 21 CFR 314.127(a)(7) are met.[15] Similarly, in oxandrolone, we concluded that geriatric labeling regarding oxandrolone's indication for weight gain that is protected by exclusivity could be omitted from the labeling of generic products.[16] We have permitted carve-outs in the context of both geriatric and, as discussed below, pediatric labeling. As explained in section II.B, a carve-out of the metformin combination data will not render the product less safe or less effective for the remaining conditions of use, as there will be no impact on the data from the clinical trials supporting the use of repaglinide as monotherapy or in combination therapy with a TZD.

B. A Split Certification Is Appropriate Because the '358 Patent Contains Composition Claims, a Product Claim, and a Method-of-Use Claim.

You also assert that allowing a split certification (a paragraph IV certification and section viii statement) with respect to a single patent appears to run counter to FDA practice. We disagree.

FDA's practice is to allow both a paragraph IV certification and a section viii statement to the same patent

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[15] June 11, 2002, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Ms. Macdonald, Ms. Jaskot, and Mr. Hurst, Docket Nos. 2001P-0495, 2002P-0191, and 2002P-0252 (Tramadol Response Letter).

[16] December 1, 2006, letter from Steven K. Galson, Director, Center for Drug Evaluation and Research, to Edward John Allera, Docket No. FDA-2005-P-0383 (Oxandrolone Response Letter).

when the patent claims both the drug (or an aspect of the drug such as the formulation or drug delivery system) and a method of using the drug. When the patent contains multiple claims, as is the case with Prandin, the ANDA applicant may file a paragraph IV certification to some claims and a section viii statement to other claims.

The Agency has previously explained that a paragraph IV certification and a section viii statement "are not overlapping, and an applicant does not have the option of making a certification under § 314.94(a)(12)(i)(A)(4) in lieu of, or in addition to, a statement under § 314.94(a)(12)(iii)" (see final rule, Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions (59 FR 50338 at 50347 (October 3, 1994)). The Agency further noted (at 50347):

> If, however, there are listed patents that present both a product and method of use claim, the applicant may file a paragraph IV certification with respect to the product patent or patent claim and a statement that the product that is the subject of the application does not involve a patented method of use with respect to the method of use patent or patent claim.

In support of your position (Petition at 4, n.8), you quote the *Purepac* decision as stating that there is a long-standing rule that for every patent, only one of two approaches — a section viii statement or a paragraph IV certification — is appropriate (Petition at 4, n.8). The *Purepac* case involved the drug gabapentin, approved to treat epilepsy, and U.S. Patent No. 5,084,479 (the '479 patent) that was listed in the

Orange Book. The '479 patent was a method-of-use patent for treating neurodegenerative diseases, which was an unapproved use of gabapentin. Purepac submitted an ANDA for gabapentin and filed a section viii statement to the '479 patent because Purepac was not seeking approval to market gabapentin for the treatment of neurodegenerative disease (Id. at 881). FDA informed Purepac that a paragraph IV certification to the '479 patent should have been submitted because the owner of the reference listed drug product claimed that the "patent covered gabapentin's use for treating epilepsy." Purepac refused to file a paragraph IV certification in place of its section viii statement to the '479 patent and sued FDA. The district court held that the "FDA should have concluded ... that the '479 patent covered gabapentin's use for treating neurodegenerative diseases" and since "Purepac sought approval for a different use ... the district court directed FDA to accept the company's section viii statement" (Id. at 881-82).

Your reliance on the *Purepac* case to support your position on repaglinide is not persuasive because gabapentin did not involve a patent that contained multiple claims for a drug substance and a method of use. At issue in the *Purepac* case was whether a paragraph IV or a section viii statement was appropriate for the method-of-use '479 patent. A combination patent with multiple claims can be evaluated claim by claim, with a paragraph IV certification being applicable to some claims and a section viii statement being applicable to other claims. A section viii statement is appropriate when a patent listed in the Orange Book "[claims] a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include

any indications that are covered by the use patent" (21 CFR 314.94(a)(12)(iii)(A)). The '358 patent for Prandin is a combination patent that claims both a drug and a method of using the drug in combination with metformin. Therefore, the correct approach for Caraco to address the '358 patent would be a paragraph IV certification to claims covering the drug (claims 1-3 and 5) and a section viii statement for the claim covering the method of using the drug (claim 4) to obtain approval for the use of repaglinide as a monotherapy treatment and as a combination therapy with TZDs.

Furthermore, FDA has permitted applicants to split certifications where a single patent contains claims either for a drug substance or drug product and a method of use or for multiple methods of use. FDA has a consistent practice of permitting other ANDA applicants to submit applications containing both a paragraph IV certification and a section viii statement to the same patent. For example, in Mylan Pharmaceuticals Inc.'s (Mylan's) ANDA 78-902 for Paroxetine Tablets, Mylan filed a paragraph III certification to U.S. Patent No. 4,721,723 and a paragraph IV certification to U.S. Patent Nos. 5,872,132, 5,900,423, 6,113,944, 6,133,289, and 6,121,291 (the '291 patent) (claim 2). A section viii statement was also filed for the '291 patent (claim 1). The Agency permitted Mylan to carve out the labeling projected by claim 2 of the '291 patent (with a section viii statement) while simultaneously challenging another method of use claim protected by the other claims of the patent. Similarly, in Barr Laboratories, Inc.'s (Barr's) ANDA for fluoxetine hydrochloride, U.S. Patent No. 4,626,549 was listed in the Orange Book as covering more than one claim described by the NDA holder as

covering different uses of fluoxetine hydrochloride. The Agency indicated that it would permit ANDA applicants to file a paragraph IV certification to the '549 patent to assert that the labeling does not infringe the patent or that the patent is invalid or unenforceable for some of the claims and also include a section viii statement to indicate that the method of use claim does not claim a use for which the ANDA applicants are seeking approval. Just as the Agency has accepted both a paragraph IV certification and a section viii statement for the same patent in the past where it claims both the drug product and an approved method of using the drug, it is acceptable for Caraco to submit both a paragraph IV certification and a section viii statement for the '358 patent.

C. Omission of the Protected Indication From the Labeling of Generic Versions of Repaglinide Does Not Render Repaglinide Less Safe and Effective for the Remaining, Nonprotected Conditions of Use.

You claim that if the information on the use of repaglinide in combination with metformin is omitted from the labeling, this drug will be less safe and effective for the remaining conditions of use (Petition at 6-11). You state that the combination therapy statement in the product labeling is crucial information, especially since repaglinide is increasingly used in combination with metformin (Petition at 8-9). You state that omitting this information ignores the progressive nature of type 2 diabetes and would give a false impression that the two drugs should not be used in combination with each other (Petition at 10). In addition, you claim that the omission of the metformin information would imply that the only approved combination therapy would be the use of repaglinide with TZDs

(Petition at 10). You state that there are a number of warnings or precautions associated with TZDs that are not present with metformin. Consequently, you claim that safety would be compromised because of the absence of labeling for metformin combination therapy. Furthermore, you argue that removal of the metformin combination, which may involve lower initial does of metformin than when metformin is used as monotherapy, would result in higher dosages of metformin when taken as a monotherapy, resulting in a higher incidence of side effects (Petition at 11). Last, you state that eliminating the data and information pertaining to the safe use of repaglinide in combination with metformin eliminates the safe and effective use of repaglinide in combination with both metformin and a TZD (Petition at 11).

As noted in section I.D above, an ANDA may be approved after omitting a patent-protected condition of use if omission of the protected information does not render the application less safe or effective for the remaining, *nonprotected* conditions of use. FDA has concluded that when information regarding the combination use of repaglinide with metformin is carved out, generic repaglinide will remain safe and effective for the remaining, nonprotected conditions of use.

When information relating to the protected, metformin combination therapy use is removed from the repaglinide labeling, the information that will appear in the generic labeling will be the information regarding the nonprotected monotherapy and combination therapy with TZDs. As mentioned in section I.A above, Novo Nordisk submitted a supplement to the Agency requesting that the Prandin labeling be changed to comply with FDA's request that all antidiabetic drug products have a simplified indication.

Effective July 14, 2008, the labeling for Prandin was revised to exclude information in the INDICATIONS AND USAGE section regarding the combination therapy use of this drug product with metformin and TZDs. As such, the INDICATIONS AND USAGE section for the generic repaglinide labeling will be identical to Prandin. Only the references to metformin combination therapy in other sections of the drug labeling will be carved out from the generic product's labeling. The remaining metformin information is contained in the CLINICAL PHARMACOLOGY section under Clinical Trials and the DOSAGE AND ADMINISTRATION section of Prandin's labeling. We have determined that carving out the metformin information in these sections of the drug labeling will not render the product less safe or effective for the remaining, nonprotected conditions of use.

The only trial described in the labeling that involved the combination of Prandin and metformin was a small trial comparing this combination to each of the monotherapies. Only 27 patients in that study received Prandin plus metformin. Despite these small numbers, the contribution of efficacy that Prandin makes to the combination of Prandin plus metformin is comparable to Prandin monotherapy. Furthermore, if a patient needs combination therapy with metformin, that patient can take the innovator drug, consistent with Prandin's labeling. In addition, no safety data from the Prandin plus metformin trial were included in the innovator label. Thus, a carve-out of the metformin combination study results will not render the product less safe or less effective for the remaining uses.

In addition, there is sufficient safety information that will remain in the labeling after the carve-out of the

metformin information. In fact, the safety information pertaining to the use of Prandin as monotherapy and in combination with TZDs is not affected by the carve-out of the metformin information because it was derived from different clinical trials. For example, the information regarding safety issues involving hypoglycemia will remain in the Prandin labeling.[17] In addition, the safety data in the Prandin label regarding the risk of serious cardiovascular events will remain after a carve-out because these data were not derived from the metformin combination therapy trials.

As mentioned above, you state that omitting the information on repaglinide and metformin coadministration ignores the progressive nature of type 2 diabetes. Progression of type 2 diabetes is well known with most patients requiring coadministration of multiple antidiabetic therapies over time, and the labeling will provide information about the use of repaglinide with TZDs. As previously mentioned, if a patient needs combination therapy with metformin, that patient can take the innovator drug, consistent with Prandin's labeling. In fact, a joint consensus statement from the American Diabetes Association and European Association for the Study of Diabetes in December 2008 (consensus statement) maintains that "more than one medication will be necessary for

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[17] Hypoglycemia has been known for many years to be a risk with the use of sulfonylureas and insulin, and this information is included in the labels for these products. Because Prandin and the sulfonylureas have a similar mechanism of action, similar language regarding hypoglycemia was inserted into the Prandin label when Prandin was approved in 1997.

the majority of patients over time."[18] The consensus statement further explains why most patients should be treated with metformin initially and that insulin or an insulin secretagog (like repaglinide) should be added later.

We reject your claim that a repaglinide drug product labeling containing only the TZD combination therapy would render the drug product less safe than Prandin. As noted previously in section II.A, FDA has reevaluated the labeling for all oral antidiabetic drugs and has eliminated the terms monotherapy and combination therapy from the INDICATIONS AND USAGE section. The recently revised label states that Prandin is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. The presence or absence of metformin information in the Clinical Trials section should have no impact on how repaglinide is used as monotherapy or in combination with a TZD. Dosing of all oral antidiabetic agents is based on findings of efficacy and tolerability in individual patients, and medications such as metformin and repaglinide are titrated based on clinical effect. Furthermore, the efficacy and safety data from repaglinide and TZD coadministration will be retained in the repaglinide label, ensuring safe and effective use of these coadministered products.

In addition, we do not believe that the absence of labeling for metformin combination therapy would result in higher dosages of metformin when taken as a monotherapy, resulting in a higher incidence of side effects. As explained above, dosing of all oral antidia-

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[18] Nathan, D, et al.: Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. *Diabetes Care* 31:1-11, 2008, p.8.

betic agents is based on findings of efficacy and tolerability in individual patients, and medications such as metformin are titrated based on clinical effect. In addition, the consensus statement contains a box insert called the "Titration of Metformin" with recommendations that are different from the label of metformin-containing products.[19] The consensus statement recommends a starting dose as low as 500 mg metformin once daily (the lowest dose in the label is 500 mg twice daily or 850 mg once daily), followed with titration every 5-7 days (the label says every two weeks). The consensus statement also recommends that patients decrease the dose for gastrointestinal symptoms but try to advance the dose at a later time.

D. FDA's Recent Responses to Citizen Petitions on a Carve-Out Issue Do Not Require That FDA Grant Your Request.

You claim that FDA's response to several recent citizen petitions regarding carve-out issues requires FDA to grant your request (Petition at 11-14). We disagree.

Our approval of an ANDA for repaglinide without information on metformin combination use would be consistent with our approvals of other generic drug products with carved-out indications and conditions of use. For example, in *Bristol-Myers Squibb*, we approved generic captopril with labeling that excluded two protected indications and corresponding protected, indication-specific dosing information. We did so even though the dosing and administration for the approved generic use was twice as high as the dosing for the carved-out indication. The D.C. Circuit held

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[19] Id., page 7.

that omission of the indications protected by exclusivity was a difference in labeling "required . . . because the drug and the listed drug are produced or distributed by different manufacturers" within the meaning of the Act (91 F.3d at 1500).

Many of FDA's recent responses to citizen petitions either can be distinguished from the Prandin carve-out situation or support the carve-out of the metformin combination therapy information because the drug product would still be safe and effective for the remaining conditions of use. For example, the citizen petition involving Rapamune (sirolimus)[20] requested that FDA refrain from approving ANDAs for sirolimus that omitted information regarding cyclosporine withdrawal from the drug product labeling before the expiration of exclusivity for the protected information. Rapamune was originally approved for use in combination with cyclosporine and corticosteroids. It was later determined that the combination of Rapamune and cyclosporine was associated with the risk of increased renal function impairment. A clinical study was performed which determined that the benefits of withdrawing cyclosporine outweighed risks of immune system reactions. The Agency determined that the inclusion of the cyclosporine withdrawal information was necessary for the safe and effective use of the drug. The carve-out described in the Rapamune Response Letter is significantly different from your Prandin petition because we have determined that Prandin can be safely used for its remaining condi-

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[20] See the September 20, 2004, letter from Steven K. Galson, Acting Director, Center for Drug Evaluation and Research, to Mr. Labson and Ms. Walsh, Docket No. (2003P-0518) (Rapamune Response Letter).

tions of use as a monotherapy and as combination therapy with TZDs.

You claim that the rationale in the citizen petition for oxandrolone[21] permitting a carve-out of the geriatric information cannot be applied to the situation involving Prandin (Petition at 12-13). The citizen petition for oxandrolone requested that the Agency refuse to approve any ANDAs for oxandrolone until the exclusivity for geriatric use expired. The petitioner for oxandrolone argued that the geriatric use information in the labeling could not be omitted because this information was necessary to ensure the safe and effective use of the drug product. You argue that the Oxandrolone Response Letter differs from Prandin because the information carved out of the generic oxandrolone labeling was simultaneously applicable to the geriatric and non-geriatric patient population (Petition at 13). With the Prandin labeling, you argue, the information proposed to be deleted from the labeling for generic versions of the drug product is not applicable to the entire repaglinide patient population all the time (Petition at 13). Furthermore, you distinguish the two situations by stating that oxandrolone had been marketed for more than 40 years without the recently added geriatric information, whereas, the Prandin product labeling has always contained the metformin information since approval by FDA.

In the Oxandrolone Response Letter, the Agency determined that the safety and effectiveness informa-

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[21] See the December 1, 2006, letter from Steven K. Galson, Director, Center for Drug Evaluation and Research, to Mr. Allera and Mr. Sullivan, Docket No. 2005P-0383 (Oxandrolone Response Letter).

tion for the geriatric use was also contained in other parts of the labeling; therefore, omission of the geriatric information would not render the drug less safe or effective. Similarly, we have determined that the omission of the metformin information in the labeling for generic repaglinide would not render the drug product less safe or effective for the remaining conditions of use. Even though the metformin information in the repaglinide labeling applies to different patient populations at different times and has been included in the product labeling since it has been on the market, we have determined that the information that remains in the labeling after the metformin information is carved out is sufficient for its safe and effective use and does not render the product less safe or effective for the remaining conditions of use (see section II.B of this response).

You also argue that the Ribavirin Response Letter supports your request in this Petition. The ribavirin petition requested that FDA refrain from approving ANDAs that do not include labeling information on the use of ribavirin with the drug PEG-Intron (peginterferon alfa-2b). The Agency determined that omission of information on the use of ribavirin with PEG-Intron would not render the drug less safe or effective. You state that FDA concluded that the PEG-Intron information could be omitted from the labeling because the generic ribavirin products would still be labeled for combination use with another related product from the same family of drugs as PEG-Intron (Intron A). You argue that FDA should not allow a carve-out of the metformin information from the generic repaglinide labeling because metformin is not chemically or pharmacologically related to any other class of antihyperglycemic agents, including TZDs

(Petition at 13). You suggest that because metformin and TZDs are not in the same class of drugs, omission of the metformin information would be confusing and affect the safety and efficacy of the drug product (Petition at 14).

Although it is true that the ribavirin example involved a carve-out of a combination therapy product (PEG-Intron) that is in the same class of drugs as the remaining combination product (Intron A), FDA based its decision to allow a carve-out of the PEG-Intron combination therapy information on the fact that the generic ribavirin labeling would be the same as the innovator product labeling for the adult use of ribavirin in combination with Intron A. When FDA approved the NDA for ribavirin, it determined that the drug product was safe and effective for the use in combination with Intron A; and the product was required to have adequate directions for the adult use of ribavirin in combination with Intron A. Therefore, FDA concluded that a generic ribavirin product (with labeling that excludes the information on the use of ribavirin in combination with PEG-Intron) would still be as safe and effective as the innovator product for the adult use of ribavirin in combination with Intron A. Similarly, FDA approved the combination use of repaglinide with metformin and with TZDs based on data derived from separate clinical trials. As such, the repaglinide product labeling contains separate information for each of the combination therapy products. As discussed in section II.B above, FDA has decided that generic repaglinide, with labeling that carves out the information on use with metformin, will be safe and effective for its remaining conditions of use.

Finally, you suggest that the citizen petition for tramadol[22] supports your argument that generic versions of repaglinide should not be permitted to carve out from the labeling the information on the combination therapy use with metformin. The tramadol petition involved labeling that omitted a protected slower titration schedule for the drug product. You argue that tramadol differs from repaglinide because the unprotected titration information that remained in the generic labeling served the same purpose as the protected, omitted titration information (Petition at 14). You argue that there is no similar unprotected labeling for a repaglinide product.

In the Tramadol Response Letter, FDA allowed information related to a 25-mg, 16-day titration dosing schedule that was protected by 3 years of marketing exclusivity and pediatric exclusivity to be carved out of the generic labeling. The protected dosing schedule was allowed to be carved out of the ANDA labeling because the unprotected 50-mg, 10-day titration dosing schedule provided adequate information. Similarly, we are allowing a carve-out of the metformin information because that information was derived from a separate clinical trial than the information regarding monotherapy or the combination use with TZDs. Therefore, repaglinide will contain sufficient information in the labeling to remain safe and effective for the remaining conditions of use.

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[22] See the June 11, 2002, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Ms. Macdonald, Ms. Jaskot, and Mr. Hurst, Docket Nos. 2001P-0495, 2002P-0191, and 2002P-0252 (Tramadol Response Letter).

E. Generic Versions of Prandin Without Combination-Use Information in the Labeling Are Not Considered New Drugs.

You state that the approval of an ANDA for repaglinide without the metformin information is not permitted because repaglinide has never been approved exclusively as a monotherapy and has always been concurrently approved for combination use with metformin (Petition at 14). It is correct that Prandin has never been approved as monotherapy only. Prandin was approved originally for both monotherapy and combination therapy with metformin, and later for combination therapy with a TZD. It is important to note, however, that each of these uses was derived from separate clinical trials. Information about the efficacy and safety of repaglinide monotherapy or repaglinide with a TZD will be retained after carve-out of the information about metformin.

As noted in section II.A and II. B above, all oral antidiabetic drugs now have the simplified indication: "Drug X is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus." Therefore, generic versions of repaglinide will contain this same indication because there is no mention of combination use with metformin in the INDICATIONS AND USAGE section of the product labeling. Removing the information in the repaglinide labeling relating to the combination use with metformin does not create a new drug not approved by FDA, because the INDICATIONS AND USAGE section will be the same and the monotherapy and combination uses were derived from different clinical trials. As mentioned in section II.B, we have determined that a carve-out of the metformin information from the drug product labeling will not com-

promise safety or effectiveness for the remaining, nonprotected conditions of use, which is the standard for evaluating a carve-out situation for generic drug products.

III. ANALYSIS OF THE CARACO PETITION

In the Caraco Petition, the petitioner requests that FDA require any ANDAs for repaglinide that include a section viii statement for claim 4 of the '358 patent (method-of-use claim for combination therapy with metformin) also include a paragraph IV certification to address claims 1-3 and 5 of the '358 patent (Caraco Petition at 2). You claim that FDA cannot approve an ANDA for repaglinide based solely on a section viii statement with regard to the '358 patent because that statement can only address claim 4 (Caraco Petition at 2). Specifically, you state that both the Act and FDA regulations provide that a section viii statement is applicable only to patent claims that describe a method of use (Caraco Petition at 2). You state that claim 4 of the '358 patent is the only claim for a method of use and that claims 1-3 and claim 5 either describe the drug composition of the product or a kit for the treatment of type 2 diabetes (Caraco Petition at 3). Therefore, you argue that ANDAs for repaglinide must submit a paragraph IV certification for claims 1-3 and 5.

We agree that the '358 patent is listed as a drug substance, a drug product, and a method-of-use patent, and are granting your request. The Act and FDA regulations allow a section viii statement only for patent claims that describe a method of use, and the section viii statement would be inapplicable to other patent claims, such as the pharmaceutical composition of a drug product. For drug composition claims, an ANDA

applicant would be required to submit the appropriate certification under section 505(j)(2)(A)(vii) of the Act. With respect to repaglinide, an ANDA applicant could not submit a section viii statement for claims 1-3 and 5 of the '358 patent because they do not involve method-of-use claims. Therefore, if an ANDA applicant chooses to submit an application with a section viii statement with respect to claim 4 of the '358 patent, the applicant would also need to submit a paragraph IV certification for claims 1-3 and 5.

IV. CONCLUSION

We have reviewed the petitions and other relevant information available to us. For the reasons stated above, we deny the Novo Nordisk Petition requesting that FDA refrain from approving any ANDAs for a repaglinide product that omits information on metformin combination therapy. With respect to the Caraco Petition, we are granting the request to require any ANDA for repaglinide that includes only a section viii statement with respect to claim 4 of the '358 patent also include a paragraph IV certification for claims 1-3 and 5.

Sincerely,

/s/ Janet Woodcock
Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

CARACO
PHARMACEUTICAL LABORATORIES, LTD.

Regulatory Affairs

MINOR AMENDMENT-FINAL APPROVAL REQUESTED

December 15, 2008

Attn: Leigh Ann Bradford
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Minor Amendment —Final Approval Requested for Repaglinide Tablets USP, 0.5 mg, 1 mg and 2 mg, ANDA # 77-571

Dear Ms. Bradford:

Caraco Pharmaceutical Laboratories Ltd. (Caraco) hereby submits a Minor Amendment-Final Approval Requested in response to Tentative Approval letter dated August 10, 2007 from Gary Buehler, Director, OGD, CDER, FDA for Repaglinide Tablets USP, 0.5 mg, 1 mg and 2 mg. Copy of FDA 'Tentative Approval' letter is enclosed.

The reference listed drug product (RLD), Prandin® (Repaglinide) Tablets of Novo Nordisk Pharmaceuticals, Inc., on which we have based our application, is currently subject to a period of patent protection. As noted in the agency's publication entitled *Approved Drug Products with Therapeutic Equivalence Evaluations*, the "Orange Book", U.S. Patent Nos. 6,677,358 (the'358 patent) RE37035 (the '035 patent) are scheduled to expire on June 12, 2018 and

March 14, 2009 respectively.

Our Original ANDA for Repaglinide Tablets USP, 0.5 mg, 1 mg and 2 mg dated February 9, 2005 contains a Paragraph III certification to the '035 patent under section 505(j)(2)(A)(vii)(III) of the act. Caraco acknowledged in its patent certification that "Caraco will not market the drug product until the U.S. Patent No. RE37035 has expired". To the best of Caraco's knowledge, '035 patent is expiring on March 14, 2009.

With respect to the '358 patent, our ANDA contains paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the act stating that the patent is invalid, unenforceable, or will not be infringed by our manufacture, use, or sale of Repaglinide Tablets, USP, 0.5 mg, 1 mg and 2 mg. Caraco notified the agency that Caraco complied with the requirements of section 505(j)(2)(B) of the act, and within the statutory 45-day timeframe litigation for infringement of the '358 patent was brought against Caraco in the U.S.Eastern Dist. Of Michigan (Novo Nordisk Pharmaceutical Inc. v. Caraco Pharmaceuticals, Ltd., Civ.Action No. 05-40188). As provided in section 505 (j)(5)(B)(iii) of the act, 30 month period was expired on August 9, 2007. The trail in the court for the summary of judgment is scheduled on January 26, 2009.

In response to the agency's labeling deficiency dated March 17, 2008, Caraco submitted a Labeling amendment on April 2, 2008 with revised patent certification (split certification) to the patent#358 which allows Caraco to carve out the information pertaining to use of Repaglinide in combination with Metformin. With final approval request

Caraco respectfully request the agency to provide written confirmation on acceptance of the split-certification and the carved label submitted by Caraco in the labeling amendment dated April 2, 2008.

Based on the aforementioned details, Caraco respectfully requests the agency to grant ***Final Approval*** to its ANDA for Repaglinide Tablets USP, 0.5 mg, 1 mg, and 2 mg, ANDA No. 77-571.

Since the time of "Tentative Approval" Caraco made the following changes to the ANDA:

Chemistry and Manufacturing Controls Information:

Residual Solvent Evaluation USP Chapter <467>

To be compliant with USP Chapter <467> for residual solvent (effective from July 1, 2008) Caraco has taken the following steps to make sure that our drug product meets current USP requirement for Residual Solvents:

- We have requested the "Residual Solvent Statements" from excipient manufacturers. Residual solvent compliance statements from the excipient manufacturer are included in **Attachment 1**. Residual Solvent Justification which contains information regarding solvents used in each ingredient and which also demonstrates that it meets ICH Q3C, criteria is also included in **Attachment 1**.

- Following inactive ingredients used in the manufacture of Repaglinide tablets contains residual solvents:

- Meglumine, USP contains Methanol
- Croscarmellose Sodium, NF contains Ethanol
- Povidone USP contains Formic acid
- Polaxamer 188 contains Ethylene glycol and 1 , 4 dioxane

Caraco developed and validated methods for the determination of residual solvents in the above inactive ingredients and the method validation reports along with the updated test methods are included in **Attachment 2.** Updated release specifications are also included in **Attachment 2.**

We have used a cumulative procedure to calculate the residual solvents levels in the drug product from the levels in the ingredients used to produce the drug product. It was observed that calculation resulted in a level below that provided in the USP general chapter and therefore no testing of the drug products for residual solvents was considered. However, Isopropyl alcohol (IPA) is used in the manufacturing of Repaglinide tablets, therefore, Repaglinide Tablets will be tested for IPA as per the specification submitted in the original ANDA

Caraco also revised the finished product release specifications to update uniformity of dosage unit acceptance criteria as per current USP. The updated release specifications and test method are included in **Attachment 3.** Caraco commits to re-assess the residual solvent justification and testing requirements in the event of change in the ingredient manufacturer and establish revised controls as required to be compliant with USP chapter <467>.

Labeling Changes:

Since the time of "Tentative Approval" the reference

listed drug (RLD), Prandin® revised the outsert labeling. Based upon the revision in RLD labeling Caraco also revised the outsert labeling.

To support the above change the following documents are included:

- A Side-by-Side Comparison of the proposed outsert labeling (Iss. 3/08 and Iss. 12/08) with differences annotated, **Attachment 4**.

- RLD package outsert for Prandin® (approved July 14, 2008), **Attachment 5**.

- The proposed package outsert for Repaglinide Tablets USP, 0.5 mg, 1 mg and 2 mg in Final Printed Labeling format is submitted electronically on a CD-ROM as **Attachment 6**.

Electronic Labeling

The electronic submission of the labeling is included in a CD-ROM, consistent with the Guidances for Industry entitled "Providing Regulatory Submissions in Electronic Format-Content of Labeling" (Issued 4/2005) as **Attachment 6**. This submission is organized in a Portable Document Format (.pdf) comprising the following:

Table of Contents: This .pdf file lists all examples of labeling included in the submission, providing a hypertext link between the documents listed in the table of contents and the corresponding PDF file and a bookmark for each item in the table of contents.

- **History pi:** This .pdf file includes the list of the labeling changes for the outsert proposed in the submission and the explanation of changes.

- **RLD pi:** This .pdf file includes Approved RLD labeling.

- **Proposed pi (Iss. 03/08):** This .pdf file includes proposed labeling for the outsert, Iss. 03/08.

- **Proposed pi (Iss. 12/08):** This .pdf file includes proposed labeling for the outsert, Iss. 12/08.

To facilitate the review, the electronic labeling also includes the proposed outsert labeling in MS Word format.

Bioequivalence Studies:

The original bioequivalence studies submitted in the original ANDA were performed by Lotus Laboratories, Bangalore, India and SPARC Bioresearch, Baroda, India. Due to delay in the FDA inspection of Contract research Organization (CRO) located in the foreign country, to avoid unwanted delay in ANDA approval as precautionary measure, Caraco initiated additional Fed and Fasted bioequivalence studies with another CRO, AAI Pharma located in the United States. Fasted BE study met the bioequivalence criteria, however, the fed study did not meet the BE criteria. The fed study was repeated by AAI and again it did not meet the BE criteria.

Due to failed fed bioequivalence study, Caraco repeated the study. This study was performed by SPARC Bioresearch, Baroda, India. This new fed bioequivalence study met the bioequivalence criteria. The abbreviated summary of failed BE studies along with the passed BE study report is provided for your review and approval. The certificate of analysis of Caraco's test product and the reference product for Repaglinide tablets along with the invitro dissolution data is provided in **Attachment 7.**

The Financial Certification and Disclosure statement FDA Form 3454 and Certification of Compliance FDA

Form 3674 are also included in **Attachment 8.**

This minor amendment is organized in 13 volumes. Volume 1 contains information pertaining to CMC changes, labeling changes and in-vitro dissolution data and certificate of analysis of Caraco test product and reference product Prandin used in the BE studies. Volume 2-13 contains in-vivo BE studies.

A copy of the Table of Contents has been provided in the front of each volume of the archival and review copies of this amendment. The Archival copy consists of Volumes 1-13 and is bound in the blue binders. The Pharmacokinetics section is bound in the required orange binders and consists of 13 volumes. The Review copy contains the Chemistry, Manufacturing and Controls information, corresponding to Volumes 1 of the Archival copy.

In Compliance with 21 CFR 314 covering FDA preapproval inspections of manufacturing sites, the Detroit District Office last inspected Caraco Pharmaceutical Laboratories, May 1 to June 11, 2008.

Caraco respectfully requests the agency to grant ***Final Approval*** to its ANDA for Repaglinide Tablets USP, 0.5 mg, 1 mg, and 2 mg, ANDA No. 77-571.

Two copies of this minor amendment have been provided, one Archival copy and one for Review. In addition we have also submitted a Field Copy to the Detroit District Office.

If you have any questions, please feel free to call me at (313) 556-4178.

Sincerely,

/s/ Veeranna Lolla
(Mr.) Veeranna Lolla, RAC
Associate Director, Regulatory Affairs

Enclosures

* * * *

[Enclosure Omitted. See JA 158 - 162]

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Novo Nordisk

December 19, 2008 1280 8 DEC 22 P3:38

BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket Nos. FDA-2008-P-0343 and FDA-2008-P-0411 – Approval of Abbreviated New Drug Applications for Repaglinide

Dear Sir or Madam:

PETITION FOR RECONSIDERATION

Novo Nordisk Inc. ("Novo Nordisk") submits this Petition for Reconsideration of the decisions of the Commissioner of Food and Drugs in Docket Nos. FDA-2008-P-0343 and FDA-2008-P-0411 ("Citizen Petition Response").

A. DECISIONS INVOLVED

Novo Nordisk requests that the Commissioner reconsider its decisions that (1) an abbreviated new drug application ("ANDA") for repaglinide that omits crucial information on metformin combination therapy, which is protected by patent and currently appears in the labeling of the innovator product, PRANDIN®, would not be less safe or effective for the remaining, non-protected conditions of use and (2) a split certification is appropriate as to U.S. Patent No. 6,677,358 ("the '358 patent") that claims, *inter alia,* repaglinide in combination with metformin.

B. ACTION REQUESTED

Novo Nordisk respectfully requests that the Commissioner refrain from approving any ANDA for repaglinide that omits information on metformin combination therapy. As explained below, not only is the Citizen Petition Response wrong on the merits, but it also is inconsistent with the arguments the Food and Drug Administration ("FDA") has advanced in *Federal Register* announcements and court filings on the subject of preemption of conflicting state laws.

C. STATEMENT OF GROUNDS

1. Background

PRANDIN is currently approved for use in monotherapy or combination therapy (with metformin or thiazolidinediones ("TZDs")) essentially for the single indication of lowering blood glucose in those suffering from type 2 diabetes. As a result of FDA's directive with respect to all oral anti-diabetic drugs to revise the *Indications and Usage* sections of their labeling to provide a single, straightforward statement that encompasses all therapy regimens for the drugs, the *Indications and Usage* section of the PRANDIN labeling presently states: "PRANDIN is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus."

As discussed in the Citizen Petition filed by Novo Nordisk ("Citizen Petition"), the original labeling for PRANDIN contained information based on studies demonstrating safety and effectiveness when PRANDIN was used both as monotherapy and in combination with metformin, a primary drug used in the treatment of type 2 diabetes when PRANDIN was in-

itially approved (and now).[1] The information on use of repaglinide as combination therapy with metformin appears pervasively throughout the labeling, including the *Clinical Trials and Dosage and Administration* sections.[2] Although the clinical trials that supported the approval of PRANDIN for repaglinide monotherapy and repaglinide in combination with metformin were separate clinical trials, this is not a situation in which two unrelated indications were evaluated separately by FDA, each on its own merits; rather, the information pertaining to the use of repaglinide as monotherapy and in combination with metformin is intertwined and, given the progressive nature of type 2 diabetes, represents the anticipated medical practice for the drug. This is consistent with FDA's current draft guidance document pertaining to the development of drugs for the treatment and prevention of diabetes, which states that "[g]iven the progressive nature of type 2 diabetes and the requirement for multiple drug therapy, the clinical development program should involve evaluation of the investigational drug as monotherapy and in combination with many other approved antidiabetic drugs."[3]

2. Novo Nordisk's Petition for Reconsideration Satisfies the Factors for *Reconsideration under 21 C.F.R. § 10.33(d).*

The public interest and the interests of justice support the Commissioner promptly granting Novo Nor-

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[1] *See* Citizen Petition, at 2-5.

[2] *See id.* at 7-9.

[3] Food and Drug Administration, Draft Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention, 8 (Feb. 2008).

disk's Petition for Reconsideration. Novo Nordisk's Petition for Reconsideration satisfies the factors for reconsideration under 21 C.F.R. § 10.33(d)(1)-(4). First, as discussed in more detail in sections C.3 – C.5 below, certain of Novo Nordisk's arguments pertaining to its repaglinide Citizen Petition were not adequately addressed in FDA's Citizen Petition Response. Second, Novo Nordisk's arguments regarding reconsideration are not frivolous and are being pursued in good faith. FDA's Citizen Petition Response failed to recognize the important differences between the situation presented by Novo Nordisk's repaglinide Citizen Petition and the precedents cited by FDA in its response. Therefore, FDA's response did not address Novo Nordisk's arguments adequately. Reconsideration is not only appropriate but necessary in these circumstances. Third, public policy supports reconsideration of FDA's response. Issues pertaining to certification of patents by ANDA applicants, as well as those pertaining to carving out information from generic labeling, are widespread at this time, and it is important to the public and the regulated industry that FDA's decisions that may have precedential value correctly apply the law. Fourth, reconsideration of these issues is not outweighed by public health interests or any other public interest. In fact, reconsideration of Novo Nordisk's arguments would serve the public health since a generic repaglinide product with labeling that omits reference to the metformin combination use is less safe and effective for the remaining, non-protected conditions of use. Moreover, FDA's decision here undermines its argument about the primacy of FDA-approved labeling in the preemption context.

3. Generic Repaglinide That Does not Contain Information Pertaining to Use in Combination with Metformin is Less Safe and Effective for the *Remaining, Non-Protected Conditions of Use.*

FDA's Citizen Petition Response asserts that generic repaglinide labeling that omits metformin combination therapy will remain safe and effective for the remaining, non-protected conditions of use.[4] Novo Nordisk disagrees with FDA's determination. As an initial matter, FDA's Citizen Petition Response appears to misconstrue the relative safety and efficacy of the remaining, non-protected conditions of use. The fact that accurate information pertaining to repaglinide monotherapy and repaglinide in combination with a TZD would remain in the generic repaglinide labeling does not mean that the product is as safe and effective as PRANDIN for the treatment of type 2 diabetes generally. As discussed in Novo Nordisk's Citizen Petition, repaglinide is increasingly used in combination with metformin such that potentially more than half of the patients who are prescribed PRANDIN are also prescribed metformin to be taken concurrently.[5] To ignore this use of repaglinide would render the product less safe or effective for the treatment of type 2 diabetes.

a. FDA's Reliance on Information Outside the Proposed Generic Repaglinide Labeling is Improper.

The FDA Citizen Petition Response relies on information outside of the proposed generic repaglinide

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[4] *See* Citizen Petition Response, at 12-14.

[5] *See* Citizen Petition, at 9.

labeling in determining that repaglinide would not be rendered less safe or effective with the omission of the metformin combination therapy information.[6] Specifically, FDA's Citizen Petition Response cites to a joint consensus statement from the American Diabetes Association and European Association for the Study of Diabetes[7] to provide information related to combination therapy. FDA's reliance on information outside of the generic repaglinide labeling to demonstrate that the generic repaglinide labeling would be no less safe or effective for the remaining, non-protected conditions of use is inappropriate and inconsistent with FDA's longstanding principles regarding approved labeling.

It is well-established that "FDA interprets the [Federal Food, Drug, and Cosmetic Act] to establish both a 'floor' and a 'ceiling'" for labeling.[8] FDA has stated repeatedly, most recently in an amicus brief in the Supreme Court pertaining to preemption, that "'[d]rug labeling serves as the standard under which FDA determines whether a product is safe and effective.'"[9] FDA further reiterated that "[l]abeling is [t]he centerpiece of risk management,' as it 'communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under

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[6] *See* Citizen Petition Response, at 13-14.

[7] *See* Nathan, D, et al., Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy, *Diabetes Care* 31:1-11 (2008) ("Joint Consensus Statement").

[8] 71 Fed. Reg. 3922, 3935 (Jan. 24, 2006).

[9] Brief for the United States as Amicus Curiae Supporting Petitioner at 11, *Wyeth* v. *Levine*, No. 06-1249 (S.Ct. June 2, 2008) (quoting 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985)).

which the product can be used safely and effectively.'"[10]

FDA has disregarded its longstanding principles regarding the purpose of approved labeling by relying on information in the Joint Consensus Statement to attempt to contradict Novo Nordisk's assertions of the necessity for repaglinide labeling to contain information pertaining to metformin combination therapy. It is telling that in none of FDA's previous carve-out decisions has FDA relied on information outside of the labeling to determine whether the omission renders the product less safe or effective for the remaining, non-protected conditions of use. Moreover, the extra-label source of information does not contain all of the relevant information that would be carved out from the generic repaglinide labeling. For example, the Joint Consensus Statement relied upon by FDA is a December 2008 update that provides a treatment algorithm that recommends metformin be used as monotherapy followed by a second medication within two to three months if lifestyle intervention and the maximal tolerated dose of metformin fail.[11] Generic repaglinide labeling that omits any mention of metformin would omit discussion of the most prominent therapy under the Joint Consensus Statement. Moreover, the treatment algorithm does not provide for the use of repaglinide under any circumstances (it is neither a tier 1 nor tier 2 medication under the Joint Consensus Statement rubric), and the Joint Consensus Statement

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[10] *Id.* (quoting 71 Fed. Reg. at 3934; *cf. Riegel* v. *Medtronic, Inc.*, 128 S. Ct. 999, 1004 (2008) ("FDA evaluates safety and effectiveness [of Class III medical devices] under the conditions of use set forth on the label.")).

[11] Joint Consensus Statement, at 8.

does not discuss repaglinide in combination with metformin at all, including the dose-sparing effects.

Assuming *arguendo* that it is appropriate for FDA to rely on the Joint Consensus Statement, that document contradicts the FDA-approved labeling for both PRANDIN and GLUCOPHAGE®, the reference listed drug for metformin. Furthermore, FDA's Citizen Petition Response states that the Joint Consensus Statement and the metformin approved labeling differ and seems to suggest following the recommendations in the Joint Consensus Statement over that in the approved labeling. More specifically, FDA states that the Joint Consensus Statement recommends a starting dose as low as 500 mg metformin once or twice daily (the lowest dose in the labeling is 500 mg twice daily, or 850 mg once daily) with a titration schedule of every five to seven days (the titration schedule in the labeling is every two weeks). FDA's apparent endorsement of a document that is inconsistent with the labeling FDA approved is strange, conflicts with FDA's preemption arguments, and provides no basis for a carve out of the metformin combination information.

b. FDA's Other Arguments Regarding the Safety and Efficacy of Generic Repaglinide are Inadequate.

First, the fact that the *Indications and Usage* section of the PRANDIN labeling no longer identifies monotherapy and combination therapy, but instead presents a single, unified indication for the treatment of type 2 diabetes does not, in itself, address whether the remaining, non-protected conditions of use are less safe or effective. It is true that there would be nothing to carve out of the *Indications and Usage* statement; however, the metformin combination therapy informa-

tion in the remaining portions of the labeling is as important as an indication statement and cannot be carved out without reducing the safety or efficacy of repaglinide.

Second, Novo Nordisk takes issue with FDA's attempts to minimize the importance of repaglinide/metformin combination therapy. Novo Nordisk disagrees with the characterization of the repaglinide/metformin combination therapy clinical trial as small. Apart from this mischaracterization, the number of patients enrolled in the combination therapy trial does not render the information gleaned from the trial any less meaningful.[12] Moreover, the size of the clinical trial does not mitigate that fact that omitting the information deprives the practitioner of the knowledge that the combination has even been studied, let alone that the combination resulted in significantly greater improvement in glycemic control as compare to either monotherapy. Novo Nordisk similarly finds no relevance to FDA's statement in its Citizen Petition Response that "the contribution of efficacy that [PRANDIN] makes to the combination of [PRANDIN] plus metformin is comparable to[PRANDIN] monotherapy."[13] Furthermore, as discussed above, FDA ignores the fact that the metformin combination therapy showed dose-sparing effects. This information would not be found in either the metformin labeling, which makes no mention of repaglinide or the use of metformin in combination with repaglinide, or the Joint Consensus Statement, even assuming that it was appro-

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[12] Novo Nordisk notes that this clinical trial was sufficient to form the basis for approval of PRANDIMET®, Novo Nordisk's fixed dose combination of repaglinide and metformin.

[13] Citizen Petition Response, at 13.

priate to look to those sources of information for this purpose.

Third, Novo Nordisk disagrees with FDA's statement that "[t]he presence or absence of metformin information in the Clinical Trials section should have no impact on how repaglinide is used as monotherapy or in combination with a TZD."[14] This statement disregards the fact that including information pertaining to TZD combination therapy while omitting information pertaining to metformin could drive prescribers toward using repaglinide in combination with a TZD rather than metformin. In light of the preference for using metformin to treat type 2 diabetes as well as the serious side effects associated with TZDs that are not present with metformin,[15] a generic repaglinide that omits metformin combination therapy could be rendered less safe or effective for the overall treatment of patients with type 2 diabetes.

c. FDA Precedent Counsels Refusing to Permit Carving Out Metformin Combination Therapy.

It is true that the majority of decisions regarding carving out protected information have permitted the information to be carved out. However, those decisions came about in situations quite different from that presented by the PRANDIN labeling, and FDA has failed to adequately explain why they apply to the PRANDIN situation. Moreover, FDA's attempt to distinguish the applicability of the RAPAMUNE decision is inadequate.

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[14] *Id.* at 14.

[15] *See* Joint Consensus Statement, at 3-4, 7-8; Citizen Petition, at 10-11.

First, with regard to the RAPAMUNE decision, FDA's only basis for distinguishing it from the present case is that FDA has "determined that [PRANDIN] can be safely used for its remaining conditions of use as a monotherapy and as combination therapy with TZDs."[16] This argument is circular. FDA does not address Novo Nordisk's discussion regarding the similarities between the situation with PRANDIN and that with RAPAMUNE.[17]

Second, with regard to *Bristol-Myers Squibb* v. *Shalala*, FDA approved generic captopril with labeling that omitted two protected indications and corresponding protected, indication-specific dosing information. As Novo Nordisk discussed in its Citizen Petition, this is very different from the case with PRANDIN because carving out all information pertaining to a separate indication is very different from carving out information pertaining to how to use the product in the only approved indication.[18] Omission of the metformin combination therapy could lead to inadequate treatment of patients with type 2 diabetes, the indication which would remain in the generic repaglinide labeling.

Third, with regard to the OXANDRIN decision, again, the only statements FDA makes in attempting to refute Novo Nordisk's argument for differentiating that decision is that FDA has already determined that omission of the metformin combination therapy would not render generic repaglinide less safe or effective for

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[16] Citizen Petition Response, at 15.

[17] *See* Citizen Petition, at 11-12.

[18] *See id.* at 15-16.

the remaining, non-protected conditions of use.[19] FDA does not address the distinguishing facts presented by Novo Nordisk, such as the fact that the concerns addressed by the protected geriatric labeling were addressed by the labeling applicable to all adults.

Fourth, with regard to the REBETOL decision, FDA fails to recognize that, unlike PEG-INTRON and INTRON-A, metformin, which is the only approved drug in the biguanide class, and TZDs are not in the same drug class, and omission of the metformin combination therapy effectively omits information pertaining to a whole class of drugs.[20] Moreover, the fact that the information pertaining to combination therapy with metformin and that pertaining to combination therapy with TZDs were derived from separate clinical trials is irrelevant to determining whether the information is necessary for safe and effective use of the product.

Fifth, with regard to the ULTRAM decision, FDA attempts to compare it to the situation with PRANDIN by stating that in both cases, the protected information was derived from a separate clinical trial.[21] As with the REBETOL case, the fact that the information derived from a separate clinical trial is irrelevant. Rather, what is important is the effect that omission of the protected information would have on the treatment of patients with type 2 diabetes.

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[19] *See* Citizen Petition Response, at 15-16.

[20] *See id.* at 16-17.

[21] *See id.* at 17.

4. FDA's Response Regarding Novo Nordisk's Argument that Approval of an ANDA for Repaglinide Without Metformin Would Compromise the *Requirement for a Listed Drug is Inadequate.*

FDA's response to Novo Nordisk's argument that approval of an ANDA for repaglinide that omits metformin combination therapy would compromise the requirement for a listed drug and create a new listed drug is inadequate. FDA's response is essentially that FDA has already determined that omission of the protected information would not compromise the safety or effectiveness of the drug.[22] The fact that the information for monotherapy and the information for metformin combination therapy were derived from separate clinical trials does not mean that FDA evaluated the propriety of approving PRANDIN for monotherapy alone. Novo Nordisk believes that this argument deserves further explanation from FDA as to why it is not persuasive.

5. *A Section viii Statement is Inappropriate as to the '358 Patent.*

Novo Nordisk does not dispute that a section viii statement is appropriate in certain circumstances or that a split certification might also be appropriate in certain circumstances. Novo Nordisk does, however, dispute that a split certification including a section viii statement is appropriate for the '358 patent.

In determining that a split certification that included a section viii statement was appropriate as to the '358 patent, FDA failed to consider the unique circumstances raised by the PRANDIN approval. With

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[22] *See id.* at 17-18.

regard to the '358 patent, a section viii statement is inappropriate since PRANDIN is effectively approved for a single use – the treatment of type 2 diabetes. It is true that the statute permits a section viii statement for a "use" covered by a patent for which the applicant is not seeking approval.[23] However, when the use that the applicant seeks to omit is subsumed within the only approved use for the drug, a section viii statement is not appropriate.[24] FDA's Citizen Petition Response fails to recognize that the "use" of repaglinide in combination with metformin is encompassed by the single method of treating type 2 diabetes.

In fact, the situation with repaglinide is more similar to the facts in *Purepac* than it is to the other precedents cited by FDA to support the notion that a split certification is appropriate.[25] As discussed in detail in the Citizen Petition, when a patent covers only one use, and that use is encompassed by the approved indication for which the application is seeking approval

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[23] *See* 21 U.S.C. § 355(j)(2)(A)(viii).

[24] *See Purepac Pharm. Co.* v. *Thompson*, 238 F. Supp. 2d 191 (D.D.C. 2002), *aff'd*, *Purepac Pharm. Co.* v. *Thompson*, 354 F.3d 877 (D.C. Cir. 2004).

[25] FDA cites the decisions regarding tramadol and oxandrolone for support for the proposition that a section viii statement is appropriate as to the '358 patent. *See* FDA Citizen Petition Response, at 9-10 (citing Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to Marcy Macdonald, et al., Docket Nos. 01P-0495/CP1, 02P-0191/CP1, & 02P-0252/CP1 (June 11, 2002); Letter from Steven K. Galson, M.D., M.P.H., Director, Center for Drug Evaluation and Research, to Edward John Allera, Buchanan Ingersoll P.C., Docket No. 2005P-0383 (Dec. 1, 2006)). Those responses, however, both dealt with 3-year Hatch-Waxman exclusivity and did not address issues related to patent certification.

of an ANDA, a section viii statement is not permitted.[26]

In the case of paroxetine tablets, the patent for which Mylan Pharmaceuticals Inc. ("Mylan") was permitted by FDA to file both a section viii statement and a Paragraph IV certification contained two claims for distinct indications or uses of the product. Claim 1, for which Mylan filed a section viii statement, covered a method of treating post traumatic stress disorder, while claim 2, for which Mylan filed a paragraph IV certification, covered a method of treating depression associated with withdrawal from heroin abuse. These two claims covered distinct uses or indications, and Mylan was only seeking approval for one of the two distinct uses. Similarly, in the case of fluoxetine hydrochloride, Barr Laboratories, Inc. was permitted by FDA to file a section viii statement for a method of treating appetite disorders. This use was distinct from the other methods of using fluoxetine hydrochloride; it was not part of a unified method of treating a single disease.

D. CONCLUSION

For the reasons discussed above, the Commissioner must promptly grant this Petition for Reconsideration, and determine that metformin combination therapy cannot be carved out from generic repaglinide labeling and a section viii statement is inappropriate as to the '358 patent.

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[26] *See* Citizen Petition, at 5-6.

Respectfully submitted,

/s/ Rosemarie R. Wilk-Orescan
Rosemarie R. Wilk-Orescan
Senior Counsel
Novo Nordisk Inc.

Novo Nordisk

December 20, 2008 1281 8 DEC 22 P3:39

BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket Nos. FDA-2008-P-0343 and FDA-2008-P-0411 – Approval of Abbreviated New Drug Applications for Repaglinide

Dear Sir or Madam:

PETITION FOR STAY OF ACTION

Pursuant to 21 C.F.R. § 10.35, Novo Nordisk Inc. ("Novo Nordisk") submits this Petition for Stay of the decisions of the Commissioner of Food and Drugs dated December 4, 2008 in Docket Nos. FDA-2008-P-0343 and FDA-2008-P-0411 (the "Citizen Petition Response").

A. DECISIONS INVOLVED

In the Citizen Petition Response, the Food and Drug Administration ("FDA") denied a citizen petition submitted by Novo Nordisk and granted a citizen petition submitted on behalf of Caraco Pharmaceutical Laboratories, Ltd. ("Caraco"). Novo Nordisk requests that FDA stay its Citizen Petition Response, and refrain from taking any regulatory action consistent with the Citizen Petition Response, including but not limited to, granting any tentative or final approval based upon the analysis contained in the Citizen Petition Response (i.e., granting any approvals for generic repaglinide that omit information on metformin combination therapy).

B. ACTION REQUESTED

Novo Nordisk requests that FDA grant the requested Petition for Stay during the pendency of Novo Nordisk's Petition for Reconsideration (filed on December 22, 2008) and any court review of FDA's Citizen Petition Response. In the event that FDA denies the instant Petition for Stay, Novo Nordisk respectfully requests that FDA stay that decision for three (3) business days, to allow Novo Nordisk an opportunity to seek emergency relief from a court.

C. STATEMENT OF GROUNDS

Novo Nordisk's substantive arguments explaining why FDA's Citizen Petition Response is incorrect are set forth fully in its Petition for Reconsideration, and those arguments are reiterated in this Petition for Stay only to the extent necessary to show that Novo Nordisk is entitled to a stay.

The public interest and the interests of justice support the Commissioner promptly granting Novo Nordisk's Petition for Stay. Novo Nordisk's Petition for Stay satisfies the requirements of 21 C.F.R. § 10.35(e)(1)-(4). First, Novo Nordisk will suffer irreparable injury in the absence of a stay. Second, Novo Nordisk's case is not frivolous and is being pursued in good faith. Third, public policy supports a stay. Fourth, reconsideration of these issues is not outweighed by public health interests or any other public interest.

1. Irreparable Injury to Novo Nordisk.

Novo Nordisk will suffer irreparable injury in the absence of a stay. U.S. Patent No. RE 37,035, to which Caraco filed a paragraph III certification, expires on March 14, 2009. Accordingly, on that date, absent a

stay, FDA could approve Caraco's abbreviated new drug application ("ANDA"), and Caraco could commence commercial marketing of generic repaglinide using FDA-approved labeling that omits crucial information and renders the drug less safe and effective for the approved use.

The irreparable injury to Novo Nordisk from this would be two-fold. First, Caraco will begin marketing a less safe and effective generic drug, the harm from which will be attributed to both the brand and generic versions of the drug, causing reputational injury to Novo Nordisk. *See Hill Dermaceuticals, Inc.* v. *U.S. F.D.A.*, 524 F. Supp. 2d 5, 12 (DD.C. 2007); *Biovail Corp.* v. *U.S. F.D.A.*, 448 F. Supp. 2d 154, 165 (D.D.C. 2006).[1] Second, generic substitution of Caraco's drug will be widespread – causing immediate and significant loss of market share to Novo Nordisk, and Novo Nordisk will not be able to recover against FDA for those damages. For these reasons, Novo Nordisk will suffer irreparable injury in the absence of a stay.

2. Novo Nordisk's Case is Meritorious and is Being Pursued in Good Faith.

a. Novo Nordisk Should Prevail on the Merits.

As set forth more fully in Novo Nordisk's Petition for Reconsideration, FDA's Citizen Petition Response was wrong on the merits and inconsistent with arguments FDA has advanced in Federal Register announcements and court filings on the subject of preemption of conflicting state laws.

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[1] In addition, a recent products liability case suggests that Novo Nordisk may be financially responsible for injury caused by Caraco's less safe and effective product. *See Conte* v. *Wyeth, Inc.*, 168 Cal. App. 4th 89 (Ct. App. 2008).

As an initial matter, FDA's Citizen Petition Response simply failed to address certain arguments advanced by Novo Nordisk, and FDA's failure to do so constitutes sufficient grounds for FDA to reconsider its Citizen Petition Response. *See, e.g., Wedgewood Vill. Pharmacy* v. *D.E.A.*, 509 F.3d 541, 549 (D.C. Cir. 2007) (An agency decision is arbitrary and capricious if it "entirely failed to consider an important aspect of the problem.").

Additionally, FDA's Citizen Petition Response is simply wrong that generic repaglinide labeling that omits metformin combination therapy will remain safe and effective for the remaining, non-protected conditions of use. This conclusion flies in the face of the undisputed fact that repaglinide is increasingly used in combination with metformin such that potentially more than half of the patients who are prescribed PRANDIN are also prescribed metformin to be taken concurrently. *See, e.g., Motor Vehicle Mfrs. Ass'n of United States, Inc.* v. *State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) (requiring "a rational connection between the facts found and the choice made").

Further, FDA's Citizen Petition Response's reliance on information outside the labeling is wrong and inconsistent with FDA precedent. *See, e.g., Ramaprakash* v. *F.A.A.*, 346 F.3d 1121, 1149-50 (D.C. Cir. 2003) (when an agency departs from its own precedents without explanation, its action is arbitrary and capricious). For all of these reasons, Novo Nordisk should prevail on its Petition for Reconsideration.

b. Novo Nordisk is Pursuing Its Case in Good Faith.

Novo Nordisk has expeditiously petitioned FDA to reconsider its Citizen Petition Response, which Novo Nordisk has already filed, and similarly plans to expeditiously seek any such further relief as may be necessary from FDA or the courts.

3. Public Polio Supports A Stay.

The Citizen Petition Response implicates serious issues of public health and FDA policy. A stay is warranted to maintain the status quo until FDA has given full and proper consideration to the arguments contained in Novo Nordisk's Petition for Reconsideration and given Novo Nordisk the opportunity to seek judicial review of FDA's decision.

4. Any Delay Resulting from a Stay is Not Outweighed by *Public Health or Other Public Interests.*

FDA has before it the information necessary to promptly reconsider its Citizen Petition Response, and thus the timing of FDA's reconsideration decision is within the agency's control. As previously noted, FDA's Citizen Petition Response implicates serious public health and FDA policy issues that deserve full and careful consideration, which consideration has not been given to date. Unless and until those issues are properly considered, public health and other public interests support a stay.

For all of these reasons, the Commissioner should grant Novo Nordisk's Petition for Stay.

D. CERTIFICATION

The undersigned certifies that, to my best know-

ledge and belief: (a) this petition includes all information and views on which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about December 4, 2008, when FDA denied Novo Nordisk's Citizen Petition. I have not received, nor do I expect to receive, payments, including cash and other forms of consideration, to file this information or its contents (other than compensation from my employer, Novo Nordisk, in the regular course of my employment). I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

/s/ Rosemarie R. Wilk-Orescan
Rosemarie R. Wilk-Orescan
Senior Counsel
Novo Nordisk Inc.

CARACO
PHARMACEUTICAL LABORATORIES, LTD.

May 29, 2009

Gary Buehler, R.Ph.
Director, Officer of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Metro Park North 2 (Room 286)
7500 Standish Place
Rockville, MD 20855

Re: ANDA No. 77-571/repaglinide

Dear Mr. Buehler:

On May 14, 2009, Martin Shimer of your office notified Caraco that Novo Nordisk Inc. and Novo Nordisk A/S recently changed the use code for U.S. Patent No. 6,677,358 in reference to Prandin (repaglinide). We write to explain why this use code change does not preclude Caraco from maintaining its section viii statement as to the '358 patent's method claim.

When construing the propriety of Caraco's section viii statement, FDA must resolve the following question: According to the information that Novo submitted to FDA, what use of repaglinide does the '358 patent cover? D.C. Circuit precedent requires FDA to consider "the entire record" when answering this question. *Purepac Pharmaceutical Company* v. *Thompson*, 354 F.3d 877, 883-885 (D.C. Cir. 2004). FDA need not be bound by a vague use code description when determining whether an ANDA applicant may carve-out a patented method of use. *See, e.g.*, FDA

Determination re amifostine, Docket No. 2006P-0410/CP1.

This record unequivocally shows, based on Novo's own representations, that the '358 patent only covers the method of combining repaglinide with metformin to treat patients with Type II diabetes—*not* the other approved uses for repaglinide (monotherapy and the combination of repaglinide with thiazolidinediones). Thus, as the FDA already has ruled in the context of Novo's Citizen Petition concerning repaglinide, "it is acceptable for Caraco to submit both a paragraph IV certification and a section viii statement for the '358 patent." FDA Letter to Orescan and Hurst, FDA-2008-P-0343-0009 (12/4/08) ("FDA Letter"). A change of course at this late date would be arbitrary and capricious.

We ask for expedited consideration of this issue to ensure that final approval of Caraco's ANDA is not unduly delayed by Novo's improper efforts to manipulate the Orange Book process.

I. Background[1]

Since April 2008, Caraco's ANDA has included a section viii statement for claim 4 of the '358 patent.[2] Claim 4 is the only method claim listed in the Orange Book for Prandin. It reads: "a method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin." From 2004-2009, the Orange Book accurately

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[1] FDA's December 4, 2008, Citizen Petition ruling contains additional background relevant to Caraco's ANDA.

[2] The ANDA also contains a Paragraph IV certification directed to the non-method claims of the '358 patent.

described this patented method as "U-546: use of repaglinide in combination with metformin to lower blood glucose."

Given its section viii statement, Caraco's ANDA includes a proposed label that carves out this patented use. In July 2008, Novo filed a Citizen Petition asking FDA to reject the proposed carve-out. Six months later, FDA denied Novo's request: "we deny the Novo Nordisk Petition requesting that FDA refrain from approving any ANDAs for a repaglinide product that omits information on metformin combination therapy." FDA Letter at 19.

In this ruling, FDA explained that repaglinide has three approved uses even though, since July 2008, the Prandin label combines these three into a single indication. FDA thus rejected Novo's argument that a section viii carve-out would be improper in light of the merged indication:

> [T]he Prandin labeling currently contains only 1 indication: as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. We disagree, however, with [Novo's] conclusions that a section viii statement is inappropriate because there is not a separate combination indication to carve out or because use in combination with metformin was approved at the time of the initial NDA approval. The statute and regulations do not require a separate indication for a carve-out. . . . *We*

> *disagree that a section viii statement, with respect to the '358 patent, is inappropriate.*

Id. at 9 (emphasis added).

In parallel litigation between Novo and Caraco, the United States District Court for the Eastern District of Michigan strongly suggested that this carve-out entitles Caraco to summary judgment on noninfringement: "if the FDA issues an approval [of Caraco's current ANDA], they will issue an approval on the label that does not, by its terms, induce infringement." Hr'g Tr. at 47:3-5 (3/27/09). The Court characterized Novo's infringement lawsuit as "an attempt by Novo Nordisk to extend the life of an expired patent [and] maintain its monopoly over a product that is covered by a patent which has expired." *Id.* at 24:2-5.[3]

In an apparent effort to circumvent FDA's ruling and avoid a judgment of noninfringement, on May 6, 2009, Novo abruptly changed the use code for the '358 patent in reference to Prandin from a valid description to an invalid one. It now reads "U-968: a method for improving glycemic control in adults with Type 2 diabetes mellitus." This use code does not describe which of the three approved methods the patent purports to cover. Yet, Novo's use code for *the very same patent* in reference to PrandiMet (a single-tablet combination of repaglinide and metformin) continues to be U-548, which specifically describes the combination. It seems that Novo hopes its more general Prandin use code will frustrate approval of Caraco's carve-out.

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[3] The Court refers here to U.S. Patent No. RE37,035, which covered the repaglinide compound. The '035 patent expired in March 2009.

II. FDA Should Approve Caraco's Section viii Statement Despite Novo's New Use Code

Novo's new use code has no bearing on whether FDA should approve Caraco's section viii statement for two independent reasons. First, the information that Novo submitted to FDA demonstrates that the '358 patent covers only one method of use—i.e., repaglinide combination therapy with metformin—and *not* any of the other labeled uses for which Caraco seeks approval. Second, Novo's use code change is untimely and thus should be completely ignored.

A. The Entire Record Demonstrates That The '358 Patent Only Covers Metformin-Repaglinide Combination Therapy

As FDA well knows, a "section viii statement indicates that a patent [listed in the Orange Book] poses no bar to approval of an ANDA because the applicant seeks to market the drug for a use other than the one encompassed by the patent." *Purepac*, 354 F.3d at 880. Thus, the first step in considering the propriety of a section viii statement is to determine what the NDA holder claims the Orange Book-listed method patent covers.

In *Purepac*, the D.C. Circuit held that FDA must consider "the entire record" in making this determination. *Id.* at 885. The *Purepac* case construed, among other things, whether FDA abused its discretion in rejecting a section viii statement for Warner-Lambert's drug gabapentin. The court summarized this issue with the following question: "According to the information that Warner-Lambert submitted to the FDA, what use of gabapentin did the '479 patent cover?"—i.e., treatment of neurodegenerative diseases or epilepsy. *Id.* at 883. The Court of Appeals

found that FDA improperly ignored repeated explicit assertions by Warner-Lambert that the '479 patent covers neurodegenerative diseases in favor of "oblique references" and "unhelpful statements" by Warner-Lambert that could be construed as asserting that the patent also covers epilepsy. *Id.* at 885. It ultimately held that FDA's action was arbitrary and capricious, particularly because "[a]t no time did Warner-Lambert tell the FDA that the patent covered a method of treating epilepsy." *Id.* at 884.

Purepac is on point. The entire record here can lead FDA to only one conclusion: Novo got it right the first time when it described its patented method for repaglinide as limited to metformin-repaglinide combination therapy.

First, until recently, the Orange Book described the '358 patent's method claim in reference to Prandin as "U-546: use of repaglinide in combination with metformin to lower blood glucose." This description, unlike the new use code, constitutes an "explicit assertion[]" of the patented method and confirms this method is limited to the metformin-repaglinide combination. *Purepac*, 354 F.3d at 885.

Second, in its Citizen Petition addressing Caraco's ANDA, Novo confirmed that "the '358 patent contains 5 claims, one of which (claim 4) *is directed to a method of treatment of NIDDM with a combination of repaglinide and metformin.*" Novo Citizen Petition 6/9/08 at 3 n.4, FDA-2008-P-0343-0001 (emphasis added). Novo took the position in its Citizen Petition that Caraco's ANDA is not "seeking approval for the method of use claimed by the '358 patent (i.e., that it is not

seeking approval for a method of treating type 2 diabetes with a repaglinide/metformin combination)." *Id.* at 4.

Third, when ruling on Novo's Citizen Petition, FDA confirmed that claim 4 of the '358 patent "concerns the method of use for the combination of repaglinide and metformin in treating type 2 diabetes." FDA Letter at 3 (citing Novo Citizen Petition at 3).

Fourth, Novo continues to use the U-546 use code for the '358 patent in reference to PrandiMet, Novo's metformin-repaglinide combination tablet. Novo thus continues to represent to FDA that the '358 patent covers only the "use of repaglinide in combination with metformin to lower blood glucose." And FDA has accepted this use code for the '358 patent. As the D.C. Circuit made clear, FDA cannot make "one decision for purposes of selecting a use code and a different decision for purposes of determining whether ANDA applicants had to submit paragraph IV certifications or section viii statements." *Purepac*, 354 F.3d at 884.

Fifth, as in *Purepac*, Novo has ***never*** taken the position that the '358 patent covers repaglinide monotherapy or in combination with thiazolidinediones, the labeled uses for which Caraco seeks approval under section viii. Nor could Novo take such a position in good faith. In another lawsuit filed on May 20—*after* Novo changed the Prandin use code—it asserts yet again that claim 4 of the '358 patent covers "a method for treating non-insulin dependent diabetes mellitus ('NIDDM') by administering repaglinide *and metformin* to a patient in need of treatment." Complaint in *Novo Nordisk et al.* v. *Mylan Pharmaceuticals Inc.*,

U.S. D.C., D. N.J., Case No. 3-09-cv-02445 (emphasis added).

Sixth, FDA has already addressed this issue in approving a proposed section viii statement for a generic amifostine product. FDA letter re amifostine dated March 13, 2008, Docket No. 2006P-0410/CP1. In that case, the NDA holder had listed U.S. Patent No. 5,994,409 in the Orange Book for Ethyol with the following use code: "Methods for using the drug product."[4] Despite this overly broad description of the protected use submitted by the NDA holder, FDA realized that the '409 patent did not cover all uses of amifostine. Instead, FDA understood that it covered the approved use of treating head and neck cancer patients, but did not cover the other approved use of treating ovarian cancer patients. Accordingly, FDA approved a section viii statement for amifostine that carved-out the protected use of treating head and neck cancer patients. FDA should take that same commonsense approach in this case.

Finally, Novo's new use code is not necessarily inconsistent with its prior representations to FDA discussed above. The new use code purports to describe claim 4 of the '358 patent as covering "*a method* for improving glycemic control in adults with Type 2 diabetes mellitus." Novo is not representing that the '358 patent covers *all methods* for improving glycemic control in adults with Type 2 diabetes mellitus, just one such method. This vague use code description does not specifically identify which approved method purportedly is patented, but it must be construed as referring to the same "method" that Novo

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[4] http://www.accessdata.fda.gov/scripts/cder/ob/docs/patterns.cfm?patent_use_code1=U&patent_use_code2=305.

previously has claimed—*i.e.*, the "use of repaglinide in combination with metformin to lower blood glucose." The record does not allow FDA to ascribe a different interpretation to Novo's "oblique" and "unhelpful" new description of the '358 patent's method claim. *Purepac*, 354 F.3d at 885.

The entire record thus demonstrates beyond question that the '358 patent's method claim covers only the combination of metformin and repaglinide and not repaglinide's other approved uses. Caraco's section viii statement remains proper despite Novo's last-second change to the Prandin use code.

B. Novo's New Use Code Is Untimely

Independent of all this, Novo's new use code is irrelevant to Caraco's ANDA because it is untimely. A new or changed patent listing must be submitted to the Orange Book staff within 30 days of approval by FDA. 21 C.F.R. § 314.53 (c)(2)(ii). Novo may contend that it changed the Prandin use code in response to an FDA directive on antidiabetic labeling from *November 2007*. But Novo changed its Prandin label in response to this directive back in July 2008. Because Caraco's ANDA already had been submitted by this time and Novo's supplemental submission was at least 10 months tardy, Caraco is not required to amend its patent certification in response to the use code change. 21 C.F.R. § 314.94 (a)(12)(vi).

III. Conclusion

In sum, Novo's changed use code does not alter Caraco's entitlement to a split-certification that includes a section viii statement, nor does it otherwise obstruct approval of Caraco's generic repaglinide ANDA. While we understand that FDA will not grant final approval until its inspections of Caraco's manufactur-

ing facilities are complete, we believe this ANDA is otherwise ready to be approved, and we ask FDA to confirm expeditiously its approval of all other aspects of Caraco's ANDA.

We would be glad to discuss this matter further at your convenience, and to provide copies of any of the documents mentioned in this letter. Thank you.

Yours very truly,

/s/ Robert Kurkiewicz
Robert Kurkiewicz

cc: Martin Shimer
James Hurst, Esq.
Charles Klein, Esq.
David S. Bloch, Esq.

WINSTON & STRAWN LLP

* * * *

David S. Bloch
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June 1, 2009

Office of Generic Drugs
Center for Drug Evaluation and Research
OGD Document Room
7500 Standish Place
Rockville, MD 20855

Attn.: Orange Book Staff

Re: 21 C.F.R. § 314.53 (f) request for correction Orange Book – U.S. Pat. No. 6,677,358 – new use code for Prandin

Dear Sirs:

On behalf of Caraco Pharmaceutical Laboratories, Ltd., we write pursuant to 21 C.F.R. § 314.53 (f) to request correction of an erroneous Orange Book submission by Novo Nordisk Inc. and Novo Nordisk A/S concerning repaglinide (Prandin). Novo has impermissibly broadened the description of the Prandin use code far beyond the scope of the only applicable method patent claim in an effort to obstruct final approval of Caraco's ANDA and summary judgment of noninfringement in Novo's parallel patent lawsuit.

U.S. Patent No. 6,677,358 contains a single method claim: "A method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment *repaglinide in combination with metformin*." From 2004-2009, the

Orange Book accurately described this patented method for Prandin as "use of *repaglinide in combination with metformin* to lower blood glucose." In May 2009, however, Novo changed the use code to read "a method for improving glycemic control in adults with Type 2 diabetes mellitus." Novo's new use code does not purport to describe the patented method itself and arguably could be construed as vaguely suggesting that the patent covers other approved *but unprotected* uses of repaglinide, including monotherapy and combination therapy with thiazolidinediones (TZDs). Novo's use code change is manifestly improper and conflicts with the rules set forth in Section 314.53. It should be corrected without delay.

I. Regulatory Background

21 C.F.R. § 314.53 (b) requires NDA holders to submit "patent information" to FDA "for each patent that claims the drug or a method of using the drug that is the subject of the new drug application . . . and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product." *See also* 21 U.S.C. § 355 (c)(2).

For method claims, this patent information includes "use codes" and specific descriptions of the methods of use contained in the applicable patents. 21 C.F.R. § 314.53 (b)(1). Use codes are intended to alert ANDA applicants to the existence of a patent that claims an approved use. *Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements, etc.*, 68 Fed. Reg. 36676, 36683 (6/18/03). So under Section 314.53 (b)(1), "[t]he applicant *shall separately identify each pending or ap-*

proved method of use and related patent claim" and "identify with specificity the section of the approved labeling that corresponds to the method of use claimed by the patent submitted."

FDA expects a high degree of specificity in these use codes: "To effectively implement the certification and section viii statement provisions set out in the statute, we must have adequate information concerning method-of-use patents." 68 Fed. Reg. at 36683. Therefore, "[t]he declarant must describe *each individual method of use* for which a patent is submitted for listing, and identify the corresponding language found in the labeling of the approved NDA that corresponds to that method of use." *Id.* at 36681 (emphasis added). This listing must be "*accurate and detailed*" [*id.*]; the applicant must provide "a description of *each* approved method of use or indication and related patent claim of the patent being submitted," along with "the specific section of the approved labeling of the drug product that corresponds to the method of use claimed by the patent" and a "*description of the patented method of use* as required for publication." 21 C.F.R. § 314.53 (c)(2)(ii)(P); *see also* Form 3542 Instructions[1]; 68 Fed. Reg. at 36683.[2] FDA's 2003 amendments to Section 314.53 were intended to ensure that NDA-holder submissions would be "more

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[1] "The use code designates a method of use patent that claims the approved indication or use of a drug product. Each approved use claimed by the patent should be separately identified in this section and contain adequate information to assist . . . ANDA applicants in determining whether a listed method of use patent claims a use for which the . . . ANDA applicant is not seeking approval."

[2] "[T]he final rule requires NDA applicants or holders or patent owners to submit *detailed information* and to certify to its correctness" (emphasis added).

informative and precise." *FDA Generic Drugs Final Rule Questions and Answers*, http://www.fda.gov/oc/initiatives/generics/ qna.html (6/12/03).

A use code's accuracy must be attested to under penalty of perjury.[3] Form 3542 specifically cautions that willfully and knowingly false statements are a criminal offense under 18 U.S.C. § 1001. *See* 68 Fed. Reg. at 36686; *see also* FDA Form 3542, p. 3. By placing this burden on the NDA-holder, Section 314.53 implements a critical component of the Hatch-Waxman statutory scheme, because it allows ANDA applicants to know precisely what methods they can carve out under section viii. But it relies to a very great extent on the good faith compliance of the NDA holder. With respect to Novo Nordisk, that reliance appears to be misplaced.

II. Procedural Background

Repaglinide is an oral antidiabetic agent. It has three approved uses: monotherapy, combination therapy with metformin, and combination therapy with TZDs.

When repaglinide was approved for use in the United States in 2004, Novo Nordisk listed two patents in the Orange Book. U.S. Patent No. RE37,035 covered the chemical formulation of repaglinide. It expired in March 2009. U.S. Patent No. 6,677,358 covers the combination of repaglinide with metformin. Claim 4

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[3] In this regard, FDA's final rule is stricter than its original proposal: "In the proposal, we stated that we had revised the declaration so that applicants would 'make careful and well-considered representations' and 'stand behind the accuracy of that information' . . .. In the final rule, we revise the statement to be more specific about the need to ensure the information is accurate." 68 Fed. Reg. at 36686.

of the '358 patent, the only method claim, is directed to a "method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin." From 2004 to May 2009, Novo's corresponding Prandin use code tracked the patent language: "U-546: use of repaglinide in combination with metformin to lower blood glucose."

Caraco is the first ANDA filer for repaglinide. In 2005, in reliance on Novo's Orange Book listings, Caraco submitted a Paragraph III certification for the '035 patent and a Paragraph IV certification as to the '358 patent. Novo sued for patent infringement shortly thereafter.

In April 2008, at FDA's suggestion, Caraco amended its ANDA to submit a Paragraph III certification as to the '035 patent, a Paragraph IV certification as to the '358 patent, and a section viii statement as to the '358 patent's method-of-use claim. Pursuant to section viii, Caraco's current ANDA label omits all reference to the patented metformin-repaglinide combination.

Three months later, Novo filed a Citizen Petition (Docket No. FDA-2008-P-0343-0001) seeking to block approval of Caraco's split certification. Novo argued that (1) metformin-repaglinide combination therapy is not a separately approved indication capable of being carved out of Caraco's label, and (2) omission of metformin-repaglinide combination therapy information from Caraco's label would be unsafe. Novo concedes in its Citizen Petition that the '358 patent claims "repaglinide in combination with metformin." *Id.* at 3.

In December 2008, FDA rejected Novo's Citizen Peti-

tion. It confirmed that Caraco's "split certification" is proper: "we have determined that a carve-out of the metformin information from the drug product labeling will not compromise safety or effectiveness for the remaining, non-protected conditions of use." FDA Letter to Orescan and Hurst (12/4/08), FDA-2008-P-0343-0009. In this response, FDA expressly addressed and rejected Novo's contention that a carve-out is improper based on FDA's November 2007 directive concerning "merged indications" for antidiabetics:

> the Prandin labeling currently contains only 1 indication: as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. We disagree, however, with your conclusions that a section viii statement is inappropriate because there is not a separate combination indication to carve out or because use in combination with metformin was approved at the time of the initial NDA approval. The statute and regulations do not require a separate indication for a carve-out.

Caraco promptly filed a motion for summary judgment in the underlying patent lawsuit, asserting that its current ANDA (with the carved-out label) cannot infringe the '358 patent. Though the Court has not yet ruled on this motion, it stated that "if the FDA issues an approval [of Caraco's current ANDA], they will issue an approval on the label that does not, by its terms, induce infringement." *Novo* v. *Caraco*, Hr'g Tr. at 47:3-5 (3/27/09). The Court characterized Novo's infringement lawsuit as "an attempt by Novo Nordisk to extend the life of an expired patent [and] maintain its monopoly over a product that is covered by a patent which has expired." *Id.* at 24:2-5.

Caraco's motion for summary judgment is fully briefed and was to be argued on June 15, 2009. It was thus a great surprise when Caraco learned that, on May 6, Novo had abruptly broadened Prandin's use code to read: "U-968: a method for improving glycemic control in adults with Type 2 diabetes mellitus." This new use code does not constitute an "accurate and detailed" description of the "individual" patented method of use set forth in claim 4 of the '358 patent. Indeed, Novo did not change the use code *for the same claim of the same patent* as applied to Novo's PrandiMet (metformin-repaglinide combi-nation) tablet. The '358 patent's use code for PrandiMet still reads "U-546: use of repaglinide in combination with metformin to lower blood glucose." It makes no sense for Novo to take the position that the same patent claim covers one use as to one product but a different use as to a different one. Novo should restore Prandin's proper use code. The '358 Patent Only Claims The Use Of Repaglinide In Combination With Metformin

III. The '358 Patent Only Claims The Use of Repaglinide In Combination With Metformin

Despite Novo's broadened use code, Novo has never taken the position that claim 4 of the '358 patent covers anything beyond the combination of repaglinide and metformin. Again, claim 4 reads: "A method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide *in combination with metformin*" (emphasis added). Novo does not—and cannot—assert in the underlying litigation or elsewhere that the '358 patent somehow covers Prandin's other approved uses (monotherapy and combination therapy with TZDs). The record is clear:

- As noted, Novo itself has, for the past 5 years, asserted in the Orange Book that the '358 patent's method claim only covers "use of repaglinide in combination with metformin to lower blood glucose."

- Novo's complaint for patent infringement against Caraco in the Eastern District of Michigan states that "[t]he '358 patent claims . . . a method for treating NIDDM by administering to a patient in need of treatment, repaglinide in combination with metformin (claim 4)." Amended Complaint ¶ 10, *Novo Nordisk et al.* v. *Caraco et al.*, U.S.D.C., E.D. Mich., Case No. 4:05 CV 40188. Novo made the same allegation, *even after changing the Prandin use code*, in its May 20 lawsuit against Mylan in the District of New Jersey. *See, e.g.*, Complaint ¶ 10, *Novo Nordisk et al.* v. *Mylan Pharmaceuticals Inc.*, U.S.D.C., D. N.J., Case No. 3-09-cv-02445.

- It has made the identical assertion in other FDA filings, and FDA has expressly relied on Novo's characterization that claim 4 of the '358 patent "concerns the method of use for the combination of repaglinide and metformin in treating type 2 diabetes." FDA Letter (FDA-2008-P-0343-0009) at 3, citing Novo's Citizen Petition at 3.

- Lastly, Novo continues to use the U-546 use code for the '358 patent in reference to PrandiMet, Novo's metformin-repaglinide combination tablet. It thus even today continues to represent to FDA that the '358 patent covers only the "use of repaglinide in combination with metformin to lower blood glucose."

In short, in every forum, Novo has consistently taken

the position—correctly—that claim 4 of the '358 patent only covers the use of repaglinide *in combination with metformin* to treat Type II diabetes. Prandin's original use code thus should be restored at once. To do otherwise would be contrary to the '358 patent's plain language and would constitute an egregious example of patent misuse. *See generally Virginia Panel Corp.* v. *Mac Panel Co.*, 133 F.3d 860 (Fed. Cir. 1997).

IV. Requested Relief

We recognize that FDA's role in connection with Orange Book use codes is limited. But FDA has powers—and responsibilities—just the same.[4] Pursuant to 21 C.F.R. § 314.53 (f), we request that the Prandin use code for U.S. Patent No. 6,677,358 be restored from to the original, and accurate, description: use of repaglinide in combination with metformin to lower blood glucose. Thank you.

Yours very truly,

/s/ David S. Bloch
David S. Bloch, Esq., M.P.H.

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[4] 68 Fed. Reg. 36676, 36683 ("it is necessary that an NDA holder submit more specific information on the approved methods of use protected by a submitted patent. Only with this information can we [FDA] determine what submission is required of the ANDA . . . applicants referencing the approved drug"), 36687 (FDA requires listing of method-of-use patents on a claim-by-claim basis so "we can verify that the certification or statement is correct, and that only the appropriate methods of use are included in the proposed labeling for the ANDA").

June 9, 2009

Dear NDA Holder:

The Food and Drug Administration (FDA) has received the enclosed challenge to your submission of patent information for your Prandin NDA.

Under the procedures established by 21 CFR 314.53(f), persons disputing accuracy or relevance of patent information submitted to the agency are requested to notify the agency in writing stating the grounds for disagreement. The agency then will request the applicable new drug application holder to confirm the correctness of the patent information submitted. Unless the application holder withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book).

Therefore, FDA requests that you review the enclosed challenge and, as soon as possible, provide FDA with written confirmation that the challenged data is correct or not correct pertaining to your Prandin NDA. Please submit any corrections that need to be made to the patent and exclusivity information addendum of the Orange Book. [Please note that patents for unapproved uses are not published in the Orange Book.] Patents to be submitted for Orange Book listing must be submitted on FDA form 3542.

Sincerely,

/s/ Mary Ann Holovac, R.Ph.
Mary Ann Holovac, R.Ph.
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
7500 Standish Place, HFD-610
Rockville, MD 20855

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[Redacted Enclosure Omitted. See JA 331 - 339 for Unredacted Version of Enclosure]

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

Civil Action No.: 4:05 CV 40188
Hon. Avern Cohn

CARACO PHARMACEUTICAL LABORATORIES, LTD.'S THIRD AMENDED ANSWER AND COUNTERCLAIM

Defendant-Counterclaim Plaintiff Caraco Pharmaceutical Laboratories, Ltd. ("Defendant" or "Caraco"), by and through its undersigned attorneys, submits the following Third Amended Answer and Counterclaim to the First Amended Complaint for Patent Infringement of Plaintiffs-Counterclaim Defendants Novo Nordisk A/S and Novo Nordisk Inc. ("Plaintiffs" or "Novo"), wherein numbered paragraphs 1-24 below correspond to the numbered paragraphs in the Amended Complaint.

1. Admitted.

2. Caraco is without information sufficient to form a belief as to the truth or falsity of the allega-

tions in paragraph 2 of the First Amended Complaint and therefore, denies them.

3. Caraco is without information sufficient to form a belief as to the truth or falsity of the allegations in paragraph 3 of the First Amended Complaint and therefore, denies them.

4. Caraco admits the allegations of paragraph 4, but states that the principal place of business of Caraco Pharmaceutical Laboratories, Ltd. is located at 115 Elijah McCoy Drive, Detroit, Michigan.

5. Admitted.

6. Caraco denies the allegations of paragraph 6 of the First Amended Complaint.

7. Admitted.

8. Caraco admits that Sun Pharmaceutical Industries, Ltd. ("Sun") and Caraco are collectively referred to as "Defendants," and states that Sun is the majority shareholder of Caraco, but denies the remaining allegations of paragraph 8 of the First Amended Complaint.

9. Caraco admits that a copy of U.S. Patent No. 6,677,358 ("the '358 patent") was attached as Exhibit A to the First Amended Complaint and that in the '358 patent, NIDDM is used as an abbreviation for non-insulin dependent diabetes mellitus. Caraco is without information sufficient to form a belief as to the truth or falsity of the remaining allegations in paragraph 9 of the First Amended Complaint and therefore, denies them.

10. Caraco denies the allegations of paragraph 10 of the First Amended Complaint as inaccurately and

incompletely paraphrasing the claims of the '358 patent.

11. Upon information and belief, Caraco admits that Plaintiffs presently market repaglinide under the trademark PRANDIN®.

12. Caraco admits that on December 22, 1997, the U.S. Food and Drug Administration approved PRANDIN® for the "use of repaglinide in combination with metformin to lower blood glucose" and admits upon information and belief, that Novo Nordisk Inc. is the holder of that approval. Caraco denies the remaining allegations of paragraph 12 of the First Amended Complaint.

13. Admitted.

14. Caraco admits that it filed the ANDA, that the ANDA is directed to repaglinide and its use and included a certification under Title 21, §355(j)(2)(A)(vii)(IV) regarding Novo Nordisk A/S's '358 patent.

15. Denied.

16. Upon information and belief, Caraco admits that it sent the Notice to Novo Nordisk and that the Notice states that the '358 patent is alleged to be not infringed, unenforceable, and/or invalid.

17. Denied.

18. Upon information and belief, Caraco admits that Sun exports metformin into the United States but denies the remaining allegations of paragraph 18 of the First Amended Complaint.

19. Caraco is without information sufficient to form a belief as to the truth or falsity of the allega-

tions in paragraph 19 of the First Amended Complaint and therefore, denies them.

20. Upon information and belief, Caraco admits that Sun currently exports metformin into the United States and that metformin is used as an antidiabetic. Caraco denies the remaining allegations of paragraph 20 of the First Amended Complaint or Caraco is without information sufficient to form a belief as to the truth or falsity of the remaining allegations in paragraph 20 of the First Amended Complaint and therefore, denies them.

21. Caraco is without information sufficient to form a belief as to the truth or falsity of the allegations in paragraph 21 of the First Amended Complaint and therefore, denies them.

22. Denied.

23. Denied.

24. Denied.

PRAYER FOR RELIEF

In response to Plaintiffs' Prayer for Relief in the First Amended Complaint:

a. Caraco denies that Plaintiffs are entitled to the relief requested in paragraph (a) of the Prayer for Relief in the First Amended Complaint.

b. Caraco denies that Plaintiffs are entitled to the relief requested in paragraph (b) of the Prayer for Relief in the First Amended Complaint.

c. Caraco denies that Plaintiffs are entitled to the relief requested in paragraph (c) of the Prayer for Relief in the First Amended Complaint.

d. Caraco denies that Plaintiffs are entitled to

the relief requested in paragraph (d) of the Prayer for Relief in the First Amended Complaint.

e. Caraco denies that Plaintiffs are entitled to the relief requested in paragraph (e) of the Prayer for Relief in the First Amended Complaint.

f. Caraco denies that Plaintiffs are entitled to the relief requested in paragraph (f) of the Prayer for Relief in the First Amended Complaint.

g. Caraco denies that Plaintiffs are entitled to the relief requested in paragraph (g) of the Prayer for Relief in the First Amended Complaint.

h. Caraco denies that Plaintiffs are entitled to the relief requested in paragraph (h) of the Prayer for Relief in the First Amended Complaint.

i. Caraco denies that Plaintiffs are entitled to the relief requested in paragraph (i) of the Prayer for Relief in the First Amended Complaint.

j. Caraco denies that Plaintiffs are entitled to the relief requested in paragraph (j) of the Prayer for Relief in the First Amended Complaint.

k. Caraco denies that Plaintiffs are entitled to the relief requested in paragraph (k) of the Prayer for Relief in the First Amended Complaint.

l. Caraco denies that Plaintiffs are entitled to the relief requested in paragraph (l) of the Prayer for Relief in the First Amended Complaint.

m. Caraco denies that Plaintiffs are entitled to the relief requested in paragraph (m) of the Prayer for Relief in the First Amended Complaint.

CARACO'S AFFIRMATIVE DEFENSES

FIRST AFFIRMATIVE DEFENSE

25. The First Amended Complaint fails to state a claim upon which relief can be granted.

SECOND AFFIRMATIVE DEFENSE

26. Caraco will not infringe any valid claim of the '358 patent under 35 U.S.C. § 271.

THIRD AFFIRMATIVE DEFENSE

27. Upon information and belief, the claims of the '358 patent are invalid for failure to comply with the statutory prerequisites of Title 35 of the United States Code, including without limitation, one or more of §§ 101, 102, 103, 111, 112, 116, 132, 135, 256, and 287.

FOURTH AFFIRMATIVE DEFENSE

28. Plaintiffs fail to state a valid claim for willful infringement.

FIFTH AFFIRMATIVE DEFENSE

29. The '358 patent was procured through inequitable conduct, rendering the patent unenforceable.

SIXTH AFFIRMATIVE DEFENSE

30. Caraco incorporates by references paragraphs 57-69, 73(d), 70, and 71 by reference.

31. The claims of the '358 patent are unenforceable due to patent misuse.

32. Plaintiffs have misused their rights under the '358 patent, including by providing FDA with a materially inaccurate and fraudulent use code description for that patent. Plaintiffs have improperly and illegally expanded the legitimate scope of the'358

patent to delay or prevent FDA approval of Caraco's ANDA, and in this fashion also have illegally extended the life of Novo's U.S. Patent No. RE37,035, which expired on March 14, 2009.

33. As a result of Plaintiffs' misuse of the '358 patent, Caraco is entitled to a declaration that all claims of the '358 patent are unenforceable.

CARACO'S COUNTERCLAIMS

Parties

34. Defendant-Counterclaim Plaintiff Caraco Pharmaceutical Laboratories, Ltd. is a corporation incorporated and existing under the laws of Michigan, and has a principal place of business located at 115 Elijah McCoy Drive, Detroit, Michigan.

35. Plaintiff-Counterclaim Defendant Novo Nordisk A/S is, upon information and belief, a Danish corporation having a place of business at Novo Alle, DK-2880 Bagsvaerd, Denmark.

36. Plaintiff-Counterclaim Defendant Novo Nordisk, Inc. is, upon information and belief, a Delaware corporation having a principal place of business 100 College Road West, Princeton, New Jersey.

Background

37. Caraco has filed Abbreviated New Drug Application ("ANDA") No. 77-571 for approval to market 0.5 mg, 1 mg, and 2 mg repaglinide tablets in the United States. Repaglinide has been approved by the FDA for the treatment of type 2 diabetes, also known as NIDDM, a chronic disease characterized by elevated levels of sugar in the blood.

38. Caraco sent a notice letter related to ANDA No. 77-571, pursuant to 21 U.S.C.

§ 355(j)(2)(A)(vii)(IV), to Novo Nordisk A/S and Novo Nordisk, Inc., on April 26, 2005. In April 2008, Caraco amended its ANDA to include a Paragraph IV certification for the non-method claims of the '358 patent (claims 1-3 and 5) and a section viii statement for the only method claim (claim 4). As of April 2008, Caraco's proposed generic repaglinide label did not include any information relating to metformin combination therapy.

39. On or about June 9, 2005, Novo Nordisk A/S ("Novo A/S") and Novo Nordisk, Inc. filed or caused to be filed a Complaint for patent infringement, which alleges that Caraco infringes the '358 patent. That complaint was served on Caraco on or about June 15, 2005.

40. The '358 patent issued from U.S. Patent Application No. 09/459,526 ("the '526 application). On or about December 13, 1999, applicants Dr. Peter Muller and Dr. Lisbeth Hemingsen filed the '526 application with the United States Patent and Trademark Office ("PTO) which claimed, *inter alia*, a method of treating patients with NIDDM by administering a combination of repaglinide with another drug that was used to treat NIDDM, metformin. Dr. Muller subsequently became the only listed inventor and applicant because of amendments to the claimed subject matter during the prosecution of the '526 application. The '526 application was assigned to Plaintiff Novo A/S and was prosecuted by attorneys at Novo Nordisk Inc.

41. Upon examination of the '526 application, the PTO Examiner rejected the claims because the prior art showed that it would have been obvious to combine repaglinide and metformin to treat patients with

NIDDM. For example, on or about October 19, 2000, the Examiner stated that the prior art "teaches combination therapy as a rational approach to the treatment of NIDDM comprising administering agents that have different mechanisms of action and different side-effect profiles."*See* C0172424-25, at C0172426.

42. Despite Plaintiffs' arguments in response to the rejection, the Examiner maintained the rejection of the claims in three more Office Actions. *See* C0172453-56; C0172469-472; and C0172535-39. For example, in the April 16, 2002 Office Action, the Examiner did not find Plaintiffs' arguments persuasive because "the prior ar[t] is replete with examples of combination therapy wherein side-effects are minimized, dosages are reduced and a more clinically beneficial outcome is observed as compared with monotherapy." *See* C0172537.

43. In response to these rejections, Plaintiffs argued that the combination of repaglinide and metformin had synergistic effects that a skilled artisan would not have predicted. *See* C0172548-52. In support of their contention, Plaintiffs relied on results from a clinical trial labeled as Example 3 in the application ("Example 3"). *See* C0172550. Plaintiffs also referred to the statement in the '526 application that "[s]urprisingly, it has been found that when repaglinide is administered together with metformin to NIDDM patients whose glycaemic control is poor on metformin alone a significant improvement in the glycaemic control is observed. More particularly, it has been found that there is a synergism between repaglinide and metformin." *See* C0172319-36 at C0172323; C0172431-34 at C0172432.

44. Because the Examiner maintained her rejection of the claims notwithstanding Example 3, Plaintiffs submitted a declaration from Dr. Jeppe Sturis, a Principal Scientist for Plaintiff Novo Nordisk A/S. In his declaration, Dr. Sturis described the results of a study in which he examined the effect of the combination of repaglinide and metformin on Zucker obese rats. *See* C0172554-57. Dr. Sturis concluded that his rat study, along with Example 3, "strongly suggest[ed] that the combination of repaglinide and metformin has synergistic properties in type 2 diabetic patients." *See* C0172556.

45. Dr. Sturis did not attach the actual study report to his declaration. That report makes it clear that the study did *not* support a finding that the rat study had any clinical relevance to the effect of the repaglinide-metformin combination in humans. In his report, which is an internal Novo document not disclosed to the PTO, Dr. Sturis stated that "[i]n conclusion, we have demonstrated synergistic effects of repaglinide and metformin on glucose tolerance in the male Zucker rat. We *speculate* that the presence of greater than additive effects *may* be clinically relevant." *See* NOVO-0028139-141 at NOVO-0028140 (emphasis added).

46. Moreover, Dr. Sturis did not say in his declaration that the repaglinide-metformin combination resulted in synergistic properties that were surprising or otherwise unexpected. Rather, the only "evidence" to support unexpected results from the combination submitted to the PTO is an attorney argument that accompanied the declaration. Specifically, Plaintiffs' attorney contended that the Examiner's rejection was rebutted by "the evidence of synergistic

and surprising results" shown in Example 3 and Dr. Sturis' study. *See* C0172548-52 at C0172551.

47. After Plaintiffs' submission of Dr. Sturis' declaration, on or about December 30, 2002, the Examiner allowed the claims directed to the combination of repaglinide and metformin "*[b]ased solely* on the Declaration submitted by Dr. Sturis and reconsideration of the synergistic effects demonstrated in Example 3." *See* C0172670-73 at C0172672 (emphasis added). In fact, Plaintiffs have conceded in this litigation that Example 3 and Dr. Sturis's declaration are the only scientific data submitted during the prosecution of the '526 application to support Plaintiffs' contention that the combination of repaglinide and metformin has synergistic effects. *See* Response of Novo Nordisk Inc. to Request for Admission No. 71.

Plaintiffs' Inequitable Conduct Before The PTO

48. As discussed in more depth in the following paragraphs, Plaintiffs misled the Examiner by not disclosing material information to her during the prosecution of the '358 patent.

49. *First*, Plaintiffs never disclosed to the PTO three clinical studies conducted by Novo A/S that directly conflicted with Plaintiffs' representation to the Examiner that "it has been found" that the combination of repaglinide and metformin had a synergistic effect:

a. On January 16, 2001, Novo A/S initiated a clinical study with a trial ID of AGEE-3010. *See* NOVO 2536342-412. The study assessed the effect on glycaemic control before and after treatment with repaglinide or repaglinide and metformin combination therapy in patients with type 2 diabetes. *See* NOVO-2536344. On or about December 2, 2002, Novo A/S

issued a final report for AGEE-3010. The final report states "[w]hen analysed by repaglinide monotherapy and repaglinide and metformin combination therapy, *the synergistic effect of combination therapy observed by Moses et al was not consistently seen in this trial.*" *See* NOVO-2536403 (emphasis added). The Moses *et al.* publication referenced in this final report contained the same data and results as described in Example 3. *See* Deposition of Robert Moses at 36:12-37:21.

b. On or about July 25, 2002, Novo A/S initiated a clinical study with a trial ID of AGEE-3018. *See* NOVO-6854351-416. The study was conducted to compare the efficacy profile of repaglinide in combination with metformin as compared to metformin or repaglinide given as monotherapy for the treatment of type 2 diabetes. *See* NOVO-6854353. On or about September 29, 2003, Novo A/S issued a final report for AGEE-3018. The final report states "[t]he results observed in this study were contrary to the study by Moses *et al* which showed that HbA1c and FPG were significantly improved in the combination therapy of repaglinide/metformin compared to treatment with either drug as monotherapy in obese type 2 diabetic subjects. *The synergistic effect of combination therapy observed by Moses et al was not consistently seen in this trial* (only between combination and repaglinide for HbA1c)." *See* NOVO-6854407 (emphasis added).

c. On or about March 6, 2002, Novo A/S initiated a clinical study with a trial ID of AGEE-1411. *See* NOVO-1321712-770. The study was conducted to compare the efficacy of metformin and repaglinide used in monotherapy with the combination therapy of metformin and repaglinide. *See* NOVO-1321713. On or about February 20, 2006, Novo A/S issued a final

report for AGEE-1411 The final report states that "[t]here was not a statistically significant difference among treatments for the change of HbA1c (%) in blood from baseline, neither for the intent to treat population, nor for per protocol population; that is, the three treatments [repaglinide monotherapy, metformin monotherapy, and the combination therapy of metformin and repaglinide] have the same effect over the patients, as the HbA1c was reduced in all treatments from visit 1 to visit 6. *See* NOVO-1321761.

50. These three clinical studies are all dated *before* the '358 patent issued on January 13, 2004, yet neither the existence nor the outcome of studies AGEE-3010, AGEE-3018, or AGEE-1411 were disclosed to the PTO during the prosecution of that patent.

51. Plaintiffs' failure to disclose these three clinical studies to the Examiner constitutes a material omission. Again, the results of these clinical trials conflict with the representations made by Novo A/S, Dr. Muller, and Dr. Sturis during the prosecution of the '358 patent that the combination of repaglinide and metformin had synergistic effect when used to treat patients with NIDDM. These were the very representations that provided the *sole* basis for overcoming the Examiners' repeated rejections of the application underlying the '358 patent.

52. In fact, one of Novo's own documents confirms that these studies were material to the prosecution of the '358 patent. In an email dated January 9, 2007, Plaintiffs' employees highlighted the importance of one of the studies, AGEE-3018, to the subject of a combination of repaglinide and metformin to treat patients with type 2 diabetes. The email con-

cerned the potential disclosure of AGEE-3018 to the FDA as part of the NN4440 project. Project "NN4440" concerns or concerned the development of a fixed combination product of repaglinide and metformin. In this email, Plaintiffs' employee Cliff Hall stated (in underlined text), "this trial appears relevant, and I don't see how we can avoid including it" in a production to FDA. *See* NOVO-1651059-61. There is no basis to believe that the study would be relevant to FDA's consideration of the NN4440 project, but not relevant to the prosecution of the '358 patent, which concerns the identical subject matter.

53. Upon information and belief, the existence and/or outcome of studies AGEE-3010, AGEE-3018, and AGEE-1411 were known to Plaintiffs' attorneys who prosecuted the '358 patent, Dr. Muller and/or Dr. Sturis. Alternatively, these individuals were deliberately ignorant of those studies. There is no credible explanation for the nondisclosure of these studies to Plaintiffs' attorneys who prosecuted the '358 patent, Dr. Muller and/or Dr. Sturis.

54. *Second*, Plaintiffs never disclosed to the PTO that one skilled in the art could not determine if a synergistic effect existed from the results of Example 3. One of the principal investigators of the study described in Example 3, Dr. Robert Moses, testified under oath that this study was unable to determine if the combination of repaglinide and metformin had synergistic effects. *See* Deposition of Robert Moses at 13:21-15:11, 41:14-42:18, and 65:24-66:11. Plaintiffs and Dr. Sturis knew this to be the case because Dr. Richard Carr, a scientist at Novo Nordisk Inc., notified Dr. Sturis, among others, in a August 24, 2000 email that there was no "mathematical proof that synergy really exists" and that such data would be

useful for patenting. *See* NOVO-6460530. Despite this knowledge, Plaintiffs affirmatively represented to the Examiner that "*it has been found* that there is a synergism between repaglinide and metformin" based on the results from Example 3. *See* C0172323 (emphasis added). Plaintiffs had no basis for such a representation. In fact, they knew it to be untrue.

55. *Finally*, as discussed above, Plaintiffs never disclosed to the PTO that Dr. Sturis himself did *not* believe that his rat study had any clinical relevance to the effect of the repaglinide-metformin combination in humans, let alone showed synergism between repaglinide and metformin. The report underlying that study – a report never disclosed to the PTO – merely said: "In conclusion, we have demonstrated synergistic effects of repaglinide and metformin on glucose tolerance in the male Zucker rat. We *speculate* that the presence of greater than additive effects *may* be clinically relevant." *See* NOVO-0028140 (emphasis added).

56. This is not the first instance in which Plaintiffs have committed inequitable conduct. On a previous occasion, Plaintiffs similarly misrepresented study results disclosed in a pharmaceutical patent application. In the August 3, 2004 decision entitled *Bio-Technology General Corp.* v. *Novo Nordisk A/S and Novo Nordisk Pharmaceuticals, Inc.*, No. Civ. 02-235-SLR, 2004 WL 1739722 (D. Del. Aug. 3, 2004), the District Court of Delaware held that Plaintiffs committed inequitable conduct by failing to inform the patent examiner that the procedure described in their patent application was, in fact, never performed, and the procedure actually failed despite repeated attempts to perform it. This finding of inequitable conduct was affirmed by the Federal Circuit

on October 5, 2005, in *Novo Nordisk Pharmaceuticals, Inc.* v. *Bio-Technology General Corp.*, 424 F.3d 1347 (Fed. Cir. 2005).

Plaintiffs' Patent Misuse In Connection With The '358 Patent Use Code

57. Plaintiffs continue to engage in inequitable and unlawful conduct with regard to the '358 patent in an effort to continue its monopoly on the now-expired repaglinide composition patent (U.S. Pat. No. RE37,035). In particular, they have illegally submitted materially misleading and incomplete information to FDA in a deliberate effort to delay or prevent approval of Caraco's ANDA, which seeks approval to market repaglinide solely for non-infringing uses.

58. FDA regulations require NDA holders like Plaintiffs to submit "patent information" to FDA "for each patent that claims the drug or a method of using the drug that is the subject of the new drug application ... and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product." 21 C.F.R. § 314.53 (b); *see also* 21 U.S.C. § 355 (c)(2). This patent information is listed in the so-called "Orange Book," one purpose of which is to provide notice to ANDA applicants of those patents an NDA holder represents cover the listed product.

59. The U.S. Federal Trade Commission was involved in the discussions leading to the current iteration of section 314.53, provided a detailed study of generic drug entry prior to patent expiration, and previously asked FDA to clarify its patent listing rules via Citizen Petition. *See, e.g.*, Citizen Petition, O1P-0248 (May 16, 2001). As FTC explained: "The

FDA has proposed to clear away unnecessary roadblocks to the approval of generic drug products. The FDA's important action addressing the competitive problems existing in the approval process for generic drugs, if promulgated and upheld, will [be] an effective way to bring the economic benefits of generic drugs to consumers more quickly. The Commission urges FDA, however, to make the proposed reforms even more effective by tightening its patent listing requirements." FTC Comments, Dkt. No. 02N-0417 (Dec. 23, 2002).

60. The NDA holder's obligation to submit patent information for method claims includes "use codes" and specific descriptions of the protected methods of use. 21 C.F.R. § 314.53 (b)(1).

61. "Use codes" are listed in the Orange Book and are intended to alert ANDA applicants to the existence of a patent that claims an approved use. *Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of [ANDAs] Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed, Final Rule*, 68 Fed. Reg. 36676, 36683 (June 18, 2003).

62. FDA expects a high degree of specificity in these use codes so that ANDA applicants may, if they so elect, carve out the protected use from its label and seek approval solely for non-protected uses by submitting what is called a "section viii statement." As FDA put it: "To effectively implement the certification and section viii statement provisions set out in the statute, we must have adequate information concerning method-of-use patents." 68 Fed. Reg. at 36683. Thus, under Section 314.53 (b)(1), "[t]he ap-

plicant *shall separately identify each pending or approved method of use and related patent claim*" and "identify *with specificity* the section of the approved labeling that corresponds to the method of use claimed by the patent submitted" (emphasis added).

63. Indeed, when submitting a use code description to FDA, the NDA holder "must describe *each individual method of use* for which a patent is submitted for listing, and identify the corresponding language found in the labeling of the approved NDA that corresponds to that method of use." *Id.* at 36681 (emphasis added).

64. This listing must be "*accurate and detailed*" [*id.*]; the applicant must provide "a description of *each* approved method of use or indication and related patent claim of the patent being submitted," along with "the specific section of the approved labeling of the drug product that corresponds to the method of use claimed by the patent" and a "*description of the patented method of use* as required for publication." 21 C.F.R. § 314.53 (c)(2)(ii)(P).

65. Form FDA 3542, the form NDA holders must complete in connection with the use code requirements, also mandates that the NDA holder attest to the accuracy of a use code under penalty of perjury and specifically cautions that willfully and knowingly false statements are a criminal offense under 18 U.S.C. § 1001. *See* 68 Fed. Reg. at 36686. The instructions to Form 3542 make clear that generic companies must be able to rely on specific use codes to determine whether a section viii statement is appropriate: "The use code designates a method of use patent that claims the approved indication or use of a drug product. Each approved use claimed by the pa-

tent should be separately identified in this section and contain adequate information to assist . . . ANDA applicants in determining whether a listed method of use patent claims a use for which the . . . ANDA applicant is not seeking approval." This instruction prevents the NDA holder from asserting a broad use code that would unnecessarily prevent ANDA applicants from seeking approval for non-protected uses.

66. By placing these strict requirements on the NDA-holder, Section 314.53 and Form FDA 3542 implement a critical component of the Hatch-Waxman statutory scheme because they allow ANDA applicants to know precisely what methods they can carve out under section viii. FDA does not construe patents, so it relies heavily on the good-faith compliance of the NDA holder to provide an accurate and detailed description of the patented method of use.

67. Here, Plaintiffs have listed the '358 patent in the Orange Book in reference to their repaglinide drug branded as Prandin and in reference to their metformin-repaglinide combination tablet branded as PrandiMet. Claim 4 of the '358 patent claims a single method: "A method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin."

68. Plaintiffs identified this method to FDA through its submission of a use code for the '358 patent specifically identifying this method. This was listed in the Orange Book entry for Prandin from 2004 to 2009 as: "U-546: use of repaglinide in combination with metformin to lower blood glucose."

69. But on or about May 6, 2009, Plaintiffs changed the use code for the '358 patent in reference

to Prandin to read: "U-968: a method for improving glycemic control in adults with Type 2 diabetes mellitus." This new use code does not describe the patented method of use. Nevertheless, an in-house Novo lawyer declared under penalty of perjury that this vague use code description is "an accurate and complete submission of patent information for the NDA or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct."

70. Plaintiffs changed this use code for the '358 patent in reference to Prandin as part of an improper effort to frustrate Caraco's ability to obtain final FDA approval of its ANDA. Contrary to the representation that Plaintiffs made to FDA under penalty of perjury, Novo's new use code (U-968) does not specifically or accurately describe the patented method of use found in claim 4 of the '358 patent—in fact, it does not describe that patented method at all. Instead, it vaguely suggests that the '358 patent is much broader in scope than it actually is, covering other approved but unpatented methods of use, including monotherapy and combination therapy with thiazolidinediones ("TZDs").

71. Plaintiffs assert that FDA should reject Caraco's section viii statement as to claim 4 of the '358 patent based on the new use code description. Plaintiffs therefore are now asserting that this patent claim covers *all* methods of using repaglinide to treat type-2 diabetes, not just metformin-repaglinide combination therapy. In so doing, Plaintiffs claim in ef-

fect that their monopoly on repaglinide (which expired with U.S. Pat. No. RE37,035 on March 14, 2009) should extend until the expiration date of the '358 patent.

72. Plaintiffs cannot assert such a position in good faith. The language of claim 4 of the `358 patent is expressly limited to the use of "repaglinide in combination with metformin" and cannot possibly be construed to cover repaglinide monotherapy or combination therapy with TZDs.

73. Indeed, up until their recent use code change, Plaintiffs have consistently maintained that claim 4 of the '358 patent covers only the metformin-repaglinide combination—the only plausible reading of that claim.

a. Until the recent use code change, Plaintiffs expressly asserted in the Orange Book in reference to Prandin that the '358 patent's method claim only covers the "use of repaglinide in combination with metformin to lower blood glucose."

b. Plaintiffs' complaint for patent infringement in the present litigation alleges that "[t]he '358 patent claims ... a method for treating NIDDM by administering to a patient in need of treatment, repaglinide in combination with metformin (claim 4)." Am. Compl. ¶ 10. Plaintiffs have taken the same position in other litigation involving the `358 patent. *See, e.g.*, Complaint ¶ 10, *Novo Nordisk et al.* v. *Mylan Pharmaceuticals Inc.*, U.S. District Court for the District of New Jersey Case No. 3-09-cv-02445.

c. Plaintiffs represented to FDA that "the '358 patent contains 5 claims, one of which (claim 4) is directed to a method of treatment of NIDDM with a combination of repaglinide and metformin." Novo

Citizen Petition, FDA-2008-P-0343-0001, at 3 n.4 (Jun. 9, 2008).

d. Plaintiffs also continue to use the original Prandin use code (U-546) for the '358 patent in reference to PrandiMet, Plaintiffs' metformin-repaglinide combination tablet. This demonstrates that Plaintiffs continue to believe, and represent to FDA, that the '358 patent covers only the "use of repaglinide in combination with metformin to lower blood glucose." Plaintiffs have made no effort to explain how their method claim can be construed one way for PrandiMet and a different way for Prandin.

74. For these reasons, Plaintiffs' conduct with regard to the '358 patent use code is abusive, fraudulent, and anticompetitive. The use code must be corrected to provide an accurate description of the single claimed method in the '358 patent and prevent any misunderstanding on the part of FDA concerning the limited breadth of the '358 patent.

JURISDICTION AND VENUE

75. This Court has jurisdiction under 28 U.S.C. §§ 1331, 1338(a), 2201, 2202, and 21 U.S.C. § 355(j).

76. Venue in this District is proper under 28 U.S.C. §§ 1391 and 1400.

COUNT I

(Noninfringement of the '358 patent)

77. Defendant-Counterclaim Plaintiff Caraco incorporates paragraphs 34-76 of its Third Amended Answer and Counterclaim by reference.

78. Novo Nordisk A/S claims to be the owner of the '358 patent.

79. Novo Nordisk, Inc. claims to be the holder of a New Drug Application for repaglinide tablets.

80. There is an actual, substantial, and continuing justiciable controversy between Caraco and Plaintiffs-Counterclaim Defendants, Novo Nordisk A/S and Novo Nordisk, Inc., regarding the infringement, validity, and enforceability of the '358 patent.

81. Caraco will not infringe any valid claim of the '358 patent under 35 U.S.C. § 271.

82. Caraco is entitled to a declaration that it will not infringe any valid claim of the '358 patent.

COUNT II

(Invalidity of the '358 patent)

83. Defendant-Counterclaim Plaintiff Caraco incorporates paragraphs 34-76 of its Third Amended Answer and Counterclaim by reference.

84. Upon information and belief, the claims of the '358 patent are invalid for failure to comply with the statutory prerequisites of Title 35 of the United States Code, including without limitation, one or more of §§ 101, 102, 103, 111, 112, 116, 132, 135, 256 and 287.

85. Caraco is entitled to a declaration that all claims of the '358 patent are invalid.

COUNT III

(Unenforceability)

86. Defendant-Counterclaim Plaintiff Caraco incorporates paragraphs 34-76 of its Third Amended Answer and Counterclaim by reference.

87. The claims of the '358 patent are unenforceable due to Plaintiffs' inequitable conduct before the PTO, as described above.

88. During the prosecution of the '358 patent, Plaintiffs, their respective attorneys involved in the prosecution of the '358 patent, Dr. Muller, and Dr. Sturis did not disclose the results of clinical studies AGEE-3010 and AGEE-3018 and the existence of clinical study AGEE-1411 to the PTO. The data and results from the clinical studies were material to the patentability of the '358 patent.

89. The data and results from the clinical studies were not cumulative of any information disclosed during the prosecution of the '358 patent.

90. Upon information and belief, Plaintiffs, their respective attorneys involved in the prosecution of the '358 patent, Dr. Muller, and Dr. Sturis were aware of the materiality of the data and results from the clinical studies, or were deliberately ignorant of those studies.

91. Plaintiffs, their respective attorneys involved in the prosecution of the '358 patent, Dr. Muller, and Dr. Sturis also did not disclose that Example 3 was insufficient to determine if the combination of repaglinide and metformin had synergistic effects. The non-disclosure of this information was material to the patentability of the '358 patent because Example 3 provided support for the sole reason for the allowance of the '358 patent, namely the alleged synergistic effects of the combination of repaglinide and metformin to patients with NIDDM, and such information is inconsistent with Plaintiffs', Dr. Muller's and Dr. Sturis's argument that Example 3 shows that there is a synergism between repaglinide and metformin.

92. Dr. Sturis also made materially misleading statements in his declaration concerning the applicability of the results from his rat study. Dr. Sturis did not disclose in his declaration his belief that his rat study may not be relevant to determine the effect of the combination of repaglinide and metformin in humans. This belief conflicts with Dr. Sturis's representation to the PTO that his rat study taken with Example 3 "strongly suggest that the combination of repaglinide and metformin has synergistic properties in type 3 diabetic patients."

93. Caraco further incorporates paragraphs 57-69, 73(d), 70, and 71 of its Third Amended Answer and Counterclaim by reference.

94. By virtue of these acts, Novo has improperly sought to extend the scope of the `358 patent and extend the life of the expired '035 patent. Its conduct in changing the Prandin use code was willful, deliberate, and malicious.

95. Caraco is therefore entitled to a declaration that the '358 patent is unenforceable due to inequitable conduct and patent misuse.

COUNT IV

(Order Requiring Correction of Use Code Under Hatch-Waxman Amendments)

96. Defendant-Counterclaim Plaintiff Caraco incorporates paragraphs 34-76 of its Third Amended Answer and Counterclaim by reference.

97. Under 21 U.S.C. § 355(j)(5)(C)(ii), Caraco seeks an order requiring Plaintiffs to correct the use code information submitted by Plaintiffs.

98. Plaintiffs' original Prandin use code for the '358 patent was: "U-546: use of repaglinide in combination with metformin to lower blood glucose."

99. On or about May 6, 2009, Plaintiffs changed the use code for the '358 patent in reference to Prandin to one with a much broader scope: "U-968: a method for improving glycemic control in adults with Type 2 diabetes mellitus." This new use code does not purport to specifically or accurately describe the patented method of use found in claim 4 of the '358 patent, as required by FDA regulations.

100. Novo's revised use code could be read as suggesting that the '358 patent covers all approved methods of using repaglinlide (including monotherapy and combination with TZDs). But the '358 patent cannot possibly be construed to cover any method of use other than "repaglinide in combination with metformin."

101. Caraco is entitled to an Order requiring Plaintiffs to correct the patent information submitted by Plaintiffs for the '358 patent's method claim on the ground that the patent does not claim the approved methods of using repaglinide as monotherapy or in combination therapy with TZDs. In particular, Plaintiffs must correct the use code for the '358 patent in reference to Prandin, submitted on or about May 6, 2009, from "U-968: a method for improving glycemic control in adults with Type 2 diabetes mellitus" to the original use code: "U-546: use of repaglinide in combination with metformin to lower blood glucose."

PRAYER FOR RELIEF

WHEREFORE, Caraco prays that the Court enter:

A. A declaratory judgment that Caraco will not infringe any valid claim of the '358 patent under 35 U.S.C. § 271;

B. A declaratory judgment that the '358 patent is invalid and, or in the alternative, a declaratory judgment that the '358 patent is unenforceable due to inequitable conduct and/or patent misuse;

C. An Order requiring Plaintiffs to correct the use code for the '358 patent in reference to Prandin, submitted on or about May 6, 2009, from "U-968: a method for improving glycemic control in adults with Type 2 diabetes mellitus" to the original use code "U-546: use of repaglinide in combination with metformin to lower blood glucose;"

D. An Order enjoining and restraining Novo Nordisk A/S and Novo Nordisk, Inc. and their officers, agents, servants, employees, attorneys, and those persons in active concert or participation with them from further charges of infringement or acts of enforcement based on the '358 patent against Caraco, its actual and prospective customers, suppliers, clinical investigators, and anyone in privity with Caraco;

E. An Order awarding Defendants costs and attorney's fees related to this litigation; and

F. An Order awarding Defendants such other further relief as the Court deems just and equitable due to the exceptional nature of this case.

Dated: June 11, 2009

* * * *

[Signature Blocks and Certificate of Service Omitted]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

JUN 16 2009

Rosemarie R. Wilk-Orescan
Senior Counsel
Novo Nordisk Inc.
100 College Road, West
Princeton, New Jersey 08540

Re: Docket Nos. FDA-2008-P-0343 and FDA-2008-P-0411

Dear Ms. Wilk-Orescan:

This letter responds to your petition for reconsideration (PRC) dated December 19, 2008, regarding the Food and Drug Administration's (FDA's) December 4, 2008, decision to deny your original citizen petition (FDA-2008-P-0343) (Original Petition) and to grant the related citizen petition submitted by Caraco Pharmaceutical Laboratories, Ltd. (Caraco) (FDA-2008-P-0411) (Caraco Petition). Your Original Petition requested that FDA refrain from approving any abbreviated new drug application (ANDA) for a repaglinide product that omits information on use of repaglinide in combination with metformin, a method of use which, according to your previously submitted patent information, was protected by Patent No. 6,667,358 (the '358 patent) and which currently appears in the labeling of the innovator product, Prandin (repaglinide). The Caraco Petition requested that FDA require that any ANDA for repaglinide that includes a section viii statement to carve out the method-of-use claim for use of repaglinide in combination with metformin also include a paragraph IV cer-

tification to address the other claims of the '358 patent.

This letter also responds to your petition for stay of action (Petition for Stay) dated December 20, 2008, requesting that FDA stay its citizen petition response in Docket Nos. FDA-2008-P-0343 and FDA-2008-P-0411, and refrain from taking any regulatory action consistent with the petition response, including granting any tentative or final approval for a generic repaglinide that omits information corresponding to the use code previously provided for the '358 patent. In the event that we deny your Petition for Stay, you request that FDA stay that decision for 3 business days to allow Novo Nordisk the opportunity to seek emergency relief from a court.

FDA has carefully considered the information submitted in your PRC, Petition for Stay, comments, and other relevant data available to the Agency. Based on our review of these materials and for the reasons described below, your PRC and Petition for Stay are denied as moot.

I. Background

In FDA's petition response dated December 4, 2008 (Citizen Petition Response), we denied your request that FDA refrain from approving any ANDA that carves out labeling corresponding to the previous use code for the '358 patent, because omission of the protected indication from the labeling of generic versions of repaglinide does not render repaglinide less safe and effective for the remaining, nonprotected conditions of use. In that same petition response, FDA granted Caraco's request that we require any ANDAs for repaglinide that include a section viii statement for the method-of-use claim for the use of repaglinide

in combination with metformin to also include a paragraph IV certification to address the other claims of the '358 patent.

You request reconsideration of the Citizen Petition Response because you disagree with FDA's determination that generic repaglinide labeling that omits information corresponding to the use code that you had previously submitted will be safe and effective for the remaining, nonprotected conditions of use. You claim that labeling that carves out the use of repaglinide with metformin makes a generic repaglinide product less safe or effective for the treatment of type 2 diabetes.

On May 6, 2009, you submitted to FDA an amendment to the use code relating to the '358 patent. The use code for the '358 patent on which we based the Citizen Petition Response stated the following: "Use of repaglinide in combination with metformin to lower blood glucose." The amendment you recently submitted has changed the use code for the '358 patent listed for Prandin to "A method for improving glycemic control in adults with type 2 diabetes mellitus."[1]

II. Discussion

As mentioned in the Citizen Petition Response, the Federal Food, Drug, and Cosmetic Act (the Act) and FDA regulations allow a generic drug product to omit from its labeling an indication or other aspect of labeling that is protected by a method-of-use patent.[2] The

---

[1] We note, by contrast, that the use code you have submitted for the same patent for PrandiMet continues to read "use of repaglinide in combination with metformin to lower blood glucose" (see FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book)).

[2] See 21 CFR 314.94(a)(8)(iv).

regulations at 21 CFR 314.127(a)(7) further provide that to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are *protected by patent* [emphasis added]," we must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining non-protected conditions of use."

FDA's role in listing patents is ministerial. FDA lists the patents submitted by the sponsor and publishes in the Orange Book the use codes that the sponsor provides. Sponsors must verify under penalty of perjury that the patent declaration represents "an accurate and complete submission of patent information" and attest that they are familiar with the requirements of 21 CFR 314.53 and that their submission complies with that regulation (21 CFR 314.53(c)(2)(i)(Q)). FDA relies on the sponsors to craft an accurate and complete description of relevant patent claims (to form the basis of the use code) and to identify the approved labeling that corresponds to those claims.[3] Because FDA lacks expertise in assessing patents, the Agency determines which labeling corresponds to a submitted patent (and thus which labeling may be available to carve out) by relying on the use code for that patent submitted by the sponsor. Because the use code for the '358 patent has changed since our issuance of the Citizen Petition Response and because our analysis and conclusions regarding labeling carveouts in that Citizen Petition Response were based on the previous use code, the factual pre-

---

[3] See FDA Form 3542 and 3542a; see also 21 CFR 314.53(c). FDA regulations provide a procedure for persons to dispute the accuracy or relevance of patent information submitted by a sponsor (see 21 CFR 314.53(f)).

dicate on which our previous response was based no longer applies. As a result, your PRC and Petition for Stay are denied as moot.

III. Conclusion

In light of the change in the factual circumstance regarding the use code for the '358 patent, your PRC and Petition for Stay are denied as moot.

Sincerely,

/s/ Jeffrey E. Shuren
Jeffrey E. Shuren, M.D., J.D.
Associate Commissioner for
Policy and Planning

Novo Nordisk

June 18, 2009

COPY BY E-MAIL
ORIGINAL BY MAIL

Mary Ann Holovac, R.Ph.
Office of Generic Drugs (HFD-610)
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

RE: PRANDIN® (repaglinide) Tablets
Orange Book Listing of U.S. Patent No. 6,677,358

Dear Ms. Holovac:

Novo Nordisk Inc. received your June 9, 2009, letter and the enclosure to that letter challenging the use code listed in the Orange Book for U.S. Patent No. 6,677,358 covering the use of PRANDIN (repaglinide) Tablets. After reviewing the challenge, and in view of the FDA's decision to merge the PRANDIN (repaglinide) label indications, Novo Nordisk has determined that the "U-968" patent use code is correct for U.S. Patent No. 6,677,358 covering the use of PRANDIN (repaglinide) tablets.

Please contact me at 609.987.5969 if you have any questions concerning this letter.

Respectfully submitted,

/s/ Rosemarie R. Wilk-Orescan
Rosemarie R. Wilk-Orescan
Senior Counsel
Novo Nordisk Inc.

cc: Gary J. Buehler, R.Ph.
Director, Office of Generic Drugs, FDA
Elizabeth H. Dickinson, Esq.
Associate Chief Counsel for Drugs
Office of Chief Counsel, FDA

Telephone Fax

ANDA-77-571

RECEIVED
AUG 03 2009
REGULATORY AFFAIRS

Center for Drug Evaluation and Research-FDA
OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773

TO: Caraco Pharmaceutical Laboratories, Ltd.
TEL: 248-556-4178

ATTN: Veeranna Lolla
FAX: 248-926-0231

FROM: Kendra Stewart
Kendra.Stewart@fda.hhs.gov
240-276-8998

Dear Sir:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Repaglinide Tablets USP, 0.5 mg, 1 mg, and 2mg.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling comments

* * * *

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-571

Dates of Submission: March 24, 2009 (amendment) and July 14, 2009 (amendment)

Applicant's Name: Caraco Pharmaceutical Laboratories, Ltd.

Established Name: Repaglinide Tablets USP, 0.5 mg, 1 mg, and 2 mg

---

LABELING DEFICIENCIES:

1. GENERAL COMMENT

Please submit an updated patent certification addressing the 6,677,358 patent and its associated Use Code, U-968.

2. CONTAINER: (100's, 500's, and 1000's all strengths)

Satisfactory in FPL, March 24, 2009 submission.

3. PACKAGE INSERT:

a. Drug-Drug Interactions: Please include the following title, "*CYP2C8 and CYP3A4 Inhibitors/Inducer*" prior to the paragraph beginning "Gemfibrozil and Itraconazole:..."

b. Add back as the first paragraph after the section titled, "Combination Trials"

Repaglinide was studied in combination with metformin in 83 patients not satisfactorily controlled on exercise, diet, and metformin alone. Repaglinide dosage was titrated for 4 to 8 weeks, followed by a 3-month maintenance period. Combination therapy with Repaglinide and metformin resulted in significantly greater improvement in glycemic control as compared to repaglinide or metformin monotherapy. HbA1c was improved by 1% unit and FPG decreased by an additional 35 mg/dL. In this study where metformin dosage was kept constant, the combination therapy of Repaglinide and metformin showed dose-sparing effects with respect to Repaglinide. The greater efficacy response of the combination group was achieved at a lower daily repaglinide dosage than in the Repaglinide monotherapy group (see Table).

c. Please also include the table "Repaglinide and Metformin Therapy: Mean Changes from Baseline in Glycemic Parameters and Weight after 4 to 5 months Treatment"

Revise your labeling, as instructed above, and submit final printed labeling electronically. In addition, please review the guidance for industry titled "Providing Regulatory Submissions in Electronic Format-Content of Labeling". Please provide the labeling in the Structured Product Labeling (SPL) format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or

weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

{See appended electronic signature page}

[redacted]m. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

* * * *

[Electronic Signature Page Omitted]

Supreme Court, U.S.
FILED
AUG 29 2011
OFFICE OF THE CLERK

No. 10-844

In the Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD., ET AL.,
PETITIONERS

v.

NOVO NORDISK A/S, *ET AL.*, RESPONDENTS

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

JOINT APPENDIX
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**Counsel of Record*

[ADDITIONAL COUNSEL LISTED ON INSIDE COVER]

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PETITION FOR A WRIT OF CERTIORARI FILED DEC. 23, 2010
CERTIORARI GRANTED JUNE 27, 2011

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 2910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Caraco Pharmaceutical Laboratories Ltd.	8/10/09
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
313 556 4178	(248) 926 0231

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
1150 Elijah McCoy Drive Detroit, MI 48202	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 77-571

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Repaglinide Tablets, USP	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		CODE NAME *(If any)*
See continuation sheet 1		
DOSAGE FORM:	**STRENGTHS:**	**ROUTE OF ADMINISTRATION:**
Tablets	1 mg and 2 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Lowers the blood glucose in patients with type 2 diabetes mellitus (NIDDM)

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)*
☐ NEW DRUG APPLICATION (NDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug: Prandin® Holder of Approved Application: Novo Nordisk Pharmaceuticals Inc

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Telephone Fax Labeling Amendment in response to FDA Deficiency letter dated August 3, 2009

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 **THIS APPLICATION IS** ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See continuation sheet 1
This site is ready for inspection

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See continuation sheet 2

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Highly Confidential - Attorneys' Eyes Only

This application contains the following items: *(Check all that apply)*

☐	1. Index
☒	2. Labeling *(check one)* ☐ Draft Labeling ☒ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. Patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Robert Kurkiewicz	Robert Kurkiewicz, Sr. V P Regulatory Affairs	8/10/09

ADDRESS (Street, City, State, and ZIP Code)	Telephone Number
1150 Elijah McCoy Drive, Detroit MI 48202	(313) 556-4178

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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Food and Drug Administration
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Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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Continuation Sheet 1 for FDA Form 356h

Telephone Fax Labeling Amendment for Repaglinide Tablets, USP, 1 mg and 2 mg

Chemical/Biochemical/Blood Product Name *(if any)*

The chemical name is S(+)2-ethoxy-4(2((3-methyl-1-(2-(1-piperidinyl) phenyl)-butyl) amino)-2-oxoethyl) benzoic acid

Establishment Information

1. **Drug substance**

Repaglinide, USP:

Sun Pharmaceutical Industries Ltd. Plot No. 25, Phase IV, G.I.D.C., Panoli – 394116, Dist. Bharuch, Gujarat, India	Drug substance manufacturer
Sun Pharmaceutical Industries Ltd. Acme Plaza, Andheri-Kurla Road Andheri (East), Mumbai - 400 059 India	Drug substance supplier

Contact: Mr. Ram Jhangiani

Phone: +91-22-8230102,
+91-22-8212128,
+91-22-8212115

Fax: +91-22-8212010

2. Drug Product Manufacturer

Sun Pharmaceutical Industries Ltd.
270 Prospect Plains Road
Cranbury, NJ 08512

A] Drug product manufacturer
B] Packaging Site
C] Finished product and stability testing site

Contact: Mr. Jitendra Doshi,
Phone: 606 495 2802
FAX: 609 495 2711

Registration # 3005551493

Continuation Sheet 2 for FDA Form 356h

Telephone Fax Labeling Amendment for Repaglinide Tablets, USP, 1 mg and 2 mg

Cross References

DMFs referenced in the current application are as follows:

Company	**DMF #**
Sun Pharmaceutical Industries Ltd.	17825
Alpha Packaging (formerly Quality Container Co.) (for bottles)	6779
Cheveron Phillips Chemical Company, LP	1016
Ampacet Corporation	8394
Van Blarcom Closures, Inc. (for CRC closures)	5828

Ineos Olefins and Polymers USA (formerly Solvay Polymers)	3720
Sunoco Chemicals	1584
Ferro Corporation	6630
Polyone Plastics	15302
Unipac Corporation	3782
Mold Rite Plastics Inc. (for non- CRC closures)	16574
Phillips Sumika Polypropylene Company	10562
Sunoco Chemicals	1584
Selig Sealing Products, Inc,	4544
Kerr Group, Inc., a subsidiary of Berry Plastics (for CRC closures)	2256
Huntsman Corporation	9988
Plastics Color Corporation	12767
Selig Sealing Products, Inc.	4544
Berry Plastics, Inc. (for non- CRC closures)	5713
The Dow Chemical Company	12603
PolyOne	18859
Selig Sealing Products, Inc.	4544

CARACO
PHARMACEUTICAL LABORATORIES, LTD.

Regulatory Affairs

TELEPHONE FAX LABELING AMENDMENT

August 10, 2009

Attn: Kendra Stewart
Division of Labeling and Program Support
Labeling Review Branch
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Telephone Fax Labeling Amendment for Repaglinide Tablets, USP, 1 mg and 2 mg, ANDA #77-571

Caraco Pharmaceutical Laboratories Ltd. (Caraco) hereby submits a Telephone Fax Labeling Amendment for the drug product Repaglinide Tablets, USP, 1 mg and 2 mg in response to letter received on August 3, 2009 from Wm Peter Rickman, Director, Division of Labeling and Program Support, OGD, CDER, FDA. A copy of the FDA letter is enclosed.

Pursuant to 21 CFR 314.96, we hereby amend our application with information regarding labeling changes. Attached please find our response to the Labeling deficiencies.

Two copies of this labeling amendment have been provided, one Archival copy and one for Review.

If you have any questions, please free to contact me at (313) 556 4105.

Sincerely,

/s/ Robert Kurkiewicz
Robert Kurkiewicz
Sr. Vice President, Regulatory Affairs

Enclosures

[Enclosure Reproduced at JA 376 - 379]

Caraco Pharmaceutical Laboratories, Ltd.
Telephone Fax Labeling Amendment to
ANDA# 77-571
Repaglinide Tablets USP, 1 mg and 2 mg

Labeling Deficiencies:

1. **GENERAL COMMENT:**

Please submit an updated patent certification addressing the 6,677,358 patent and its associated Use Code, U-968.

Response:

Caraco Pharmaceutical Laboratories, Ltd. (Caraco) acknowledges Agency's comment to submit an updated patent certification addressing the 6,677,358 patent and its associated Use Code, U-968. We understand from Martin Shimer, however, that the Director of the Office of Generic Drugs in consultation with FDA counsel is still considering the enclosed letter I sent to Gary Buehler on May 29, 2009 as **Attachment 1**. That letter explained why Novo Nordisk Inc. and Novo Nordisk A/S's recent use code change for U.S. Patent No. 6,677,358 (the '358 patent) in reference to Prandin (repaglinide) should not prevent or delay Agency approval of Caraco's ANDA for generic repaglinide, which seeks to carve-out references in the label to the patented repaglinide-metformin combination in accordance with a section viii statement.

As discussed in the May 29 letter, the entire record of Novo's own representations to FDA about the scope of its '358 patent lead to one conclusion: that this patent's method claim is limited to the use of repaglinide in combination with met-

formin to treat patients with type 2 diabetes. Novo has never told FDA that its patent covers the other approved uses for repaglinide—i.e., monotherapy and in combination with thiazolidinediones (TZDs)—for which Caraco seeks approval. FDA thus has no basis to reject Caraco's ANDA on the basis that Novo's patent covers those other approved uses. *See Purepac Pharmaceutical Company* v. *Thompson,* 354 F.3d 877, 883-885 (D.C. Cir. 2004).

In fact, Novo recently clarified the limited scope of its '358 patent in related litigation pending before the United States District Court for the Eastern District of Michigan, thus conclusively putting this issue to rest. During a motion and pretrial hearing on July 15, 2009, Caraco's counsel suggested that a claim construction (or *Markman*) hearing may be necessary with regard to the '358 patent's method claim (claim 4) to resolve any ambiguity as to that claim's reach. In response, Novo's counsel readily conceded in open court that the '358 patent's method claim covers only the method of using repaglinide that Caraco seeks to carve out of its label pursuant to its section viii statement, i.e., the method of using repaglinide in combination with metformin. Below is the relevant colloquy:

> **MR. KLEIN** [for Caraco]: This dispute [concerning the propriety of Novo's use code change] might concern issues of validity to the extent there is some dispute as to the scope of Claim 4 of the '358 patent. I thought throughout this case that the parties agreed that the '358 patent and particularly Claim 4 covered only a combina-

> tion of metformin with repaglinide. If Novo Nordisk is taking the position that Claim 4 covers repaglinide monotherapy or repaglinide in combination with TZD's, we are going to need to have a *Markman* hearing before the trial to resolve the dispute as to the scope of Claim 4.
>
> **MR. SITZMAN** [for Novo]: Your Honor, that is not our position and has never been our position. Mr. Klein knows, and we have maintained our position, that the patent's scope covers exactly what it says, which is the combination – a method of treating Type 2 diabetes with the combination of repaglinide and metformin.

7/15/09 Hrng Tr. at 45-46 (pertinent pages enclosed as **Attachment 2**). This representation by Novo to the Court removes any doubt as to whether Novo is taking the position that the '358 patent covers the two unpatented approved methods of using repaglinide for which Caraco seeks approval in its ANDA. As Novo's counsel succinctly put it, Novo is not taking that position and it has never been its position.

For this additional reason, Novo's amended use code in no way alters Caraco's entitlement to a split-certification that includes a section viii statement with regard to the two approved, non-patented uses, nor does it otherwise obstruct approval of Caraco's generic repaglinide ANDA. We thus request that FDA expeditiously approve Caraco's ANDA so we can get a less expensive generic repaglinide product to the public as soon as possible and suggest that you consult with Mr.

Shimer on this issue. We would be glad to discuss this matter further at your convenience.

2. CONTAINER (100s, 500s, and 1000s all strengths):

Satisfactory in FPL, March 24, 2009 submission.

Response:

Caraco acknowledges that the container labels of Repaglinide Tablets USP, 1 mg and 2 mg are satisfactory in final print as of March 24, 2009.

3. PACKAGE INSERT:

a. Drug-Drug Interactions; Please include the following title, "CYP2C8 *and* CYP3A4 *Inhibitors/inducer*" prior to the paragraph beginning "Gemfibrozil and Itraconazole...,"

Response:

Caraco acknowledges Agency's comment to include the title "CYP2C8 and CYP3A4 Inhibitors/inducer" prior to the paragraph beginning "Gemfibrozil and Itraconazole....". However the title "CYP2C8 and CYP3A4 Inhibitors/inducer" was included in the Package Outsert of Repaglinide Tablets USP, 1 mg and 2 mg, Iss. 6/09 provided in the Labeling Amendment submitted on July 14, 2009.

The proposed package outsert for Repaglinide Tablets USP, 1 mg and 2 mg in Final Printed Labeling format is submitted electronically on a CD-ROM as **Attachment 3** for your ready reference.

b. Add back as the first paragraph after the section titled, "Combination Trials"

Repaglinide was studied in combination with metformin in 83 patients not satisfactorily controlled on exercise, diet, and metformin alone. Repaglinide dosage was titrated for 4 to 8 weeks, followed by a 3-month maintenance period. Combination therapy with Repaglinide and metformin resulted in significantly greater improvement in glycemic control as compared to repaglinide or metformin monotherapy. HbA1c was improved by 1% unit and FPG decreased by an additional 35 mg/dL. In this study where metformin dosage was kept constant, the combination therapy of Repaglinide and metformin showed dose-sparing effects with respect to Repaglinide. The greater efficacy response of the combination group was achieved at a lower daily repaglinide dosage than in the Repaglinide monotherapy group (see Table).

c. Please also include the table 'Repaglinide and Metformin Therapy: Mean Changes from Baseline in Glycemic Parameters and Weight after 4 to 5 months Treatment"

Response:

Please refer to the response under General Comment

[Enclosure Reproduced at JA 321 - 330]

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants.

SEALED TRANSCRIPT

Civil Action No.: 05-40188
Hon. Avern Cohn

HEARING ON PLAINTIFFS' MOTION TO DISMISS CARACO'S FOURTH COUNTERCLAIM AND MOTION TO STRIKE CARACO'S SIXTH AFFIRMATIVE DEFENSE

Wednesday, July 15, 2009

* * * *

[Appearances Omitted]

* * * *

[*44]

it. This answer isn't complete in itself. I mean this, it may be, to a sophisticate understandable.

And then from that we get:

> "If the answer to 4.2 is 'yes,' also provide the information on the indication or method of use for the Orange Book 'Use Code' description. Use: (Submit the description of the approved indication or method of use that you propose FDA include as the 'use code' in the Orange Book using no more than 240 total characters including spaces.)"

And originally you said, "A method for improving glycemic - - no

> "Use of repaglinide in combination with metformin to lower blood glucose."

Very simple and very direct. And in the new one you have got it all changed to:

> "A method for improving glycemic control in adults with Type 2 diabetes mellitus."

That seems to me to be a substantive change, not a reformulation. That's something different than you told them the first time.

[*45]

Isn't that what you are complaining about?

MR. KLEIN: Precisely, Your Honor.

THE COURT: And you are telling me there is nobody that can deal with that.

MR. KLEIN: Your Honor, Mr. Sitzman has not cited any FDA authority that would allow FDA to change the use code.

THE COURT: Well, I suggest at this point, we are not going to get a decision today, that you all order a copy of the record and supplement it with the documents I want to see and any further argument

you want to make, and I suggest to Caraco that they may have to reformulate their counterclaim.

MR. KLEIN: Your Honor, may I raise one other matter?

THE COURT: Yeah.

MR. KLEIN: You asked earlier whether this dispute concerned issues of validity at all?

THE COURT: Yeah.

MR. KLEIN: This dispute might concern issues of validity to the extent there is some dispute as to the scope of Claim 4 of the '358 patent. I thought throughout this case that the parties agreed that the '358 patent and particularly Claim 4 covered only a combination of metformin with repaglinide. If Novo Nordisk is taking the position

[*46]

that Claim 4 covers repaglinide monotherapy or repaglinide in combination with TZD's, we are going to need to have a *Markman* hearing before the trial to resolve the dispute as to the scope of Claim 4.

MR. SITZMAN: Your Honor, that is not our position and has never been our position. Mr. Klein knows, and we have maintained our position, that the patent's scope covers exactly what it says, which is the combination -- a method of treating Type 2 diabetes with the combination of repaglinide and metformin.

THE COURT: Well, if that's true, then --

MR. SITZMAN: Yes.

THE COURT: -- the way the use code is formulated it covers repaglinide, you say, alone, no refer-

ence to metformin, and that in effect extends the life of the expired patent because it continues to give you a monopoly. That's a bad word, I know, in patent jargon. The exclusive right -- the right to exclude others. That's the right formulation. The right to exclude others from selling repaglinide. That you have got -- your exclusivity as to repaglinide continues. That's what you have accomplished by the use code and that's what he's complaining about, and he says that's patent misuse because you have gotten, in effect, a renewal or an extension of the -- what was that reissue patent number?

* * * *

[*55]

the reason why there is a reference in this form that dates back as early as Your Honor has pointed out.

THE COURT: Possibly, possibly, but she NDA associated with that patent is a different NDA. It's the NDA for the combination.

Anyhow, do you have anything more?

MR. SITZMAN: No, Your Honor. I appreciate the Court's indulgence today.

MR. KLEIN: No, Your Honor. Thank you.

THE COURT: Thank you. We are in recess.

(Proceedings concluded at 3:38 p.m.)

* * * *

[Certification Omitted]

Sitzman, Michael A.

From: Klein, Chuck [CKlein@winston.com]

Sent: Monday, August 17, 2009 2:47 PM

To: Avern_Cohn@mied.uscourts.gov

Cc: Sitzman, Michael A.

Subject: RE: Novo Nordisk, et al v. Caraco Pharmaceutical, et al (05-40188)

Attachments: Pages from C0209154.pdf

Dear Judge Cohn,

It appears that Mr. Sitzman has misconstrued the Court's August 12 question to counsel. We did not interpret the Court's question as implying that the '358 patent has expired, as Mr. Sitzman argues. Instead, we read the Court's email as asking Mr. Sitzman to provide authority supporting Novo's decision to submit its Form 3542 amendment in May 2009 under the circumstances of this case. Mr. Sitzman has not addressed this question, so we will.

As a preliminary matter, the regulations authorized Novo to make its February 2006 Form 3542 submission for the '358 patent because that patent covers an FDA-approved method of using the referenced drug. 21 C.F.R. § 314.53(b). Under the regulations, that method patent is properly listed in the Orange Book even though, as the Court notes in its email, Novo's patent covering the repaglinide compound has expired.

But the regulations did *not* authorize Novo's May 2009 Form 3542 amendment. That amendment was untimely. The regulations expressly state that any Form 3542 must be submitted "[w]ithin 30 days after the date of approval of [the NDA] or supplement." 21

C.F.R. § 314.53(c)(2)(R)(ii). Novo argues that it amended its Form 3542 in reference to Prandin in May 2009 to address a supplement to its NDA approved by FDA ten months earlier, in July 2008. This Form 3542 amendment falls far beyond the 30-day window in the regulations. Caraco thus takes the position before the FDA that the Agency should ignore Novo's amended use code description for this reason, and also because Novo has never told FDA that the '358 patent covers the two approved repaglinide uses for which Caraco seeks approval. Attached is the latest correspondence on this issue, which reflects that FDA has not yet reached a final Agency determination on whether to approve Caraco's split-certification notwithstanding the changed use code description -- an issue entirely distinct from that before the Court.

The issue before the Court is whether Novo should be compelled to correct its new use code description. The answer is yes. As Caraco has explained in its briefs, the regulations, the Federal Register, and Form 3542's instructions all make it clear that a use code narrative must accurately describe each approved method of use for the referenced drug covered by a patent listed in the Orange Book. The purpose of this requirement is to allow FDA to determine whether a generic applicant has properly applied to market the referenced drug solely for non-patented uses in accordance with "section viii" of the Hatch-Waxman Act. Novo concedes that its changed use code description does not accurately reflect the scope of the '358 patent. Yet, Novo has cited no authority to support its interpretation of the regulations. Nor has Novo attempted to justify the timing of its belated Form 3542 amendment.

Importantly, FDA has not in any way approved of

Novo's use code amendment, and Caraco certainly is not asking the Court to overrule any FDA decision. On the contrary, as the Court knows, FDA views its role in administering the Orange Book as strictly ministerial. It does not offer opinions on whether a use code description itself comports with the regulatory requirements, or instead is fraudulent and anticompetitive as Caraco alleges. See 21 C.F.R. § 314.53 (t). That determination falls squarely within the province ofthe Court. For the reasons discussed in Caraco's briefs opposing Novo's motion to dismiss and Caraco's corresponding motion for summary judgment on misuse and the Hatch-Waxman counterclaim, the Court has ample authority under the Hatch-Waxman Act and the traditional patent misuse defense to address the straightforward question at issue here—i.e., whether the regulations require Novo's use code narrative to describe the approved method of use covered by the '358 patent or, as Novo argues, allow NDA holders to manipulate the Orange Book process to delay generic competition. Caraeo has the law squarely on its side, leaving Novo with mere rhetoric.

Best regards,

Chuck Klein

From: Sitzman, Michael A. [mailto:MSitzman @gibsondunn.com]

Sent: Friday, August 14, 2009 1:07 PM

To: Avern_Cohn@mied.uscourts.gov

Cc: Klein, Chuck

Subject: RE: Novo Nordisk, et al v. Caraco Pharmaceutical, et al (05-40188)

Dear Judge Cohn:

Thank you for your email. It appears that there is a significant misunderstanding as to the issue date and expiration date of the patent-in-suit (the '358 patent), its first appearance in the Orange Book, and the significance of the various forms required by the FDA. This misunderstanding serves only to underscore the issue raised and addressed in Novo Nordisk's pending motion to dismiss; namely, that matters of Agency practice and procedure for which Congress has not created a cause of action are not subject to review by a District Court. We respectfully submit that given the lack of jurisdiction, this Court need not and should not engage in trying to decipher FDA process and procedure, or reviewing FDA decisions and actions.

With respect to the Court's specific questions, the '358 patent issued in January 2004 and does not expire until 2018. Three weeks after it issued, Novo Nordisk submitted a 3542 Form to the FDA that referenced the '358 patent. (Tab 5). Following discussions with the FDA in early 2009 and based on the FDA's decision to merge the approved indications for Prandin, Novo Nordisk amended the use code for the '358 patent on May 6, 2009. (Tab 12). Last week, the FDA directed Caraco to change its certification and label in accordance with the new use code. The FDA has rejected all of Caraco's arguments that the use code should be changed or ignored -- the very same arguments it is asking you to consider.

It is undisputed that only two things currently stand in the way of Caraco getting final approval from the FDA for its ANDA: 1) Caraco needs to change its certification in accordance with the FDA's instructions of

last week; and 2) Caraco needs to receive final approval for their proposed manufacturing facility. If Caraco feels that the FDA is treating it unfairly, its remedy is to sue the FDA, not lead this Court into reversible error by asking it to *effectively overrule the FDA in a proceeding where the FDA is not a party and where Congress has not vested this Court with jurisdiction.*

If you have any further questions concerning this matter, please do not hesitate to contact us.

Very truly yours,

Mike Sitzman

From: Lori_VanHove@mied.uscourts.gov [mailto:Lori_VanHove@mied.uscourts.gov] **On Behalf Of** Avern_Cohn@mied.uscourts.gov

Sent: Wednesday, August 12, 2009 10:53 AM

To: Sitzman, Michael A.

Cc: CKlein@winston.com

Subject: Novo Nordisk, et al v. Caraco Pharmaceutical, et al (05-40188)

Counsel:

As I read the FDA 3542 forms from Novo:

1. Novo filed three (3) FDA 3542a forms under N DA 20-741 for Prandin/Repaglinide, signed November 17, 2003, for three (3) different patents, two (2) of which expired on September 05,2006, and U.S. Patent No. RE37,035, which expired on March 14,2009.

2. Novo filed an FDA 3542 under NDA 20-741 for Prandin/Repaglinide signed February OS, 2006, for

U.S. Patent No. 6,677,3588.

3. Novo filed an FDA 3542 under NDA 20-741 for Prandin/Repaglinide signed May 06,2009, for U.S. Patent No. 6,677,358.

4. Novo filed an FDA 3542 under NDA 22-386 for Prandimet (Repaglinide/Metformin HC1) tablets/repaglinide/metformin HC1 signed October 01, 2008, for U.S. Patent No. 6,677,358.

I do not recall seeing an explanation of how a Form FDA 3542 can be filed under an NDA for a drug for which the patent has expired, i.e., filing under the '358 Patent and under NDA 20-741, or do I recall seeing any FDA rule allowing for a new Form 3542 in the circumstances here.

Have I missed something? Please advise.

Avern Cohn
United States District Judge
313-234-5160

* * * *

[Email Disclaimer Notices Omitted]

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

CONFIDENTIAL
SUBJECT TO PROTECTIVE ORDER

Civil Action No.: 2:05 CV 40188
Hon. Avern Cohn

DECLARATION OF ROBERT A. DORMER

FILED UNDER SEAL PURSUANT TO PROTECTIVE ORDER (DOCKET NO. 40)

I, Robert A. Dormer, hereby declare:

1. I am a resident of Virginia. I respectfully submit this declaration in opposition to the Motion by Defendant Caraco Pharmaceutical Laboratories, Ltd. for Summary Judgment on its Fourth Counterclaim and Sixth Affirmative Defense. I have personal knowledge of the facts set forth herein, and if called upon to testify, I could and would competently testify thereto.

2. I am a Director of Hyman, Phelps & McNamara, P.C., a Professional Corporation ("HPM"), located at 700

Thirteenth Street, N.W., Suite 1200, Washington, D.C. 20005. Prior to entering private practice in 1979, I was the Associate Chief Counsel for Enforcement and Associate Chief Counsel for Radiological Health at the U.S. Food and Drug Administration ("FDA"). Prior to the FDA, I was an attorney for the White House Special Action Office for Drug Abuse Prevention and the National Institute on Drug Abuse.

3. HPM has served as regulatory counsel for Novo Nordisk Inc. since 1993, providing counsel with regard to multiple drug products, including PRANDIN® and PrandiMet®. HPM has provided Novo Nordisk with advice and counsel regarding its June 2008 Citizen Petition requesting that the FDA refrain from approving any ANDA for repaglinide that omits from its product label information about the approved use of repaglinide in combination with metformin, as well as its submission in May 2009 of a proposed change to the use code narrative for PRANDIN®.

4. On December 4, 2008, the FDA issued a Response denying Novo Nordisk's Citizen Petition. Having reviewed the FDA Response, we believed that there were significant compelling grounds upon which Novo Nordisk could and should seek reconsideration. With our advice and counsel, on December 22, 2008, Novo Nordisk submitted a Petition for Reconsideration of the FDA Response and a Petition for Stay of Action. The Petition for Reconsideration and Petition for Stay were not immediately ruled upon by the FDA. By February 2009, there was still no decision by the FDA on either Petition.

5. At the direction of Novo Nordisk, I and another attorney from HPM met with four attorneys from the FDA's Office of Chief Counsel (Jeff Senger, Acting

Chief Counsel, Rick Blumberg, Deputy Chief Counsel for Litigation, Kim Dettelbach, Associate Chief Counsel for Drugs, and Julie Finegan, General Attorney) on February 25, 2009. The principal purpose of the meeting was to advise the FDA that Novo Nordisk was considering what actions it could or should take with FDA given the current state of affairs.

6. During the meeting, a discussion ensued about the revised labeling for PRANDIN® approved by the FDA in July 2008. I explained that the FDA had merged all of the indications for PRANDIN® into a unitary statement and that there were no longer separate indications in the label for each approved use. I explained that the patented use claimed by U.S. Patent No. 6,677,358 (the "'358 patent") was now subsumed into the unitary indication.

7. At that point, one of the FDA attorneys inquired about the use code for PRANDIN®. Ms. Dettelbach asked me what the current use code was for the '358 patent. I replied that the use code was the combination use with metformin, but that Novo Nordisk was considering submitting a new Form FDA 3542 to amend the use code to reflect the language of the new approved indication for PRANDIN®. None of the FDA attorneys objected or raised any issue about Novo Nordisk amending its use code.

I hereby declare under penalty of perjury that the foregoing is true and correct.

Executed this 9th day of September 2009 in Washington, DC.

/s/ Robert A. Dormer
Robert A. Dormer

* * * *

[Certificate of Service Omitted]

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

CONFIDENTIAL
SUBJECT TO PROTECTIVE ORDER

Civil Action No.: 2:05 CV 40188
Hon. Avern Cohn

DECLARATION OF JAMES C. SHEHAN

FILED UNDER SEAL PURSUANT TO PROTECTIVE ORDER (DOCKET NO. 40)

I, James C. Shehan, hereby declare:

1. I am a resident of the State of New York. I am Vice President and General Counsel of Novo Nordisk Inc. I respectfully submit this declaration in opposition to the Motion by Defendant Caraco Pharmaceutical Laboratories, Ltd. ("Caraco") for Summary Judgment on its Fourth Counterclaim and Sixth Affirmative Defense. I have personal knowledge of the facts set forth herein, and if called upon to testify, I could and would competently testify

thereto.

2. Novo Nordisk A/S is the owner of U.S. Patent No. 6,677,358 (the "'358 patent").

3. In May 2009, Novo Nordisk Inc. submitted an FDA Form 3542 to propose an amended use code narrative for PRANDIN® and to make a minor unrelated correction to information previously submitted to the FDA. Members of my staff and I made the decision to make those changes, and I signed the submission on behalf of Novo Nordisk. A copy of the May 2009 submission is attached hereto as Exhibit A.

4. I understand that Caraco has alleged that Novo Nordisk's submission of the proposed new use code narrative for PRANDIN® was made without any "reasonable business justification" and "fraudulent." Caraco Third Amended Answer and Counterclaim, ¶ 32 (Dkt. 309); Caraco Brief in Support of Motion for Summary Judgment at 13 (Dkt. 317). I respectfully dispute these allegations as unfounded and baseless. As explained in more detail below, Novo Nordisk had multiple legitimate business reasons for submitting the proposed new use code narrative for PRANDIN® and it did so in good faith.

I. Novo Nordisk Amended The Use Code Narrative To Reflect A Change That Was Made By FDA In The Approved Labeling For PRANDIN®

5. Prior to 2008, the "Indications and Usage" section of the approved label for PRANDIN® contained the following separate indication for approved uses of repaglinide in combination therapy: "PRANDIN is also indicated for combination therapy use (with metformin or thiazolidinediones) to lower blood glucose in patients whose hyperglycemia could not be controlled by diet and exercise, plus

monotherapy with metformin, sulfonylureas, repaglinide, or thiazolidinediones." In late November 2007, the FDA Division of Metabolism and Endocrinology Products advised Novo Nordisk that it had independently decided to replace the separate indications for PRANDIN® with a new unitary indication. Novo Nordisk complied with the FDA directive and submitted a proposed label with the new indication on January 11, 2008. On July 14, 2008, the FDA approved a new PRANDIN® label that eliminated all separate indications for PRANDIN® — whether for monotherapy or combination therapy — and replaced them with the following single approved indication: "PRANDIN is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus."

6. In its May 2009 submission on FDA Form 3542, Novo Nordisk proposed an amended use code narrative that tracks the approved indication in the new PRANDIN® label: "A method for improving glycemic control in adults with type 2 diabetes mellitus." Exhibit A at 3.

7. The FDA assigned use code U-968 to the proposed amended use code narrative and published the U-968 use code and narrative in its "Orange Book."

8. The FDA has never raised any issue or concern about Novo Nordisk's new use code narrative. In June 2009, Novo Nordisk did receive a request from FDA to confirm the accuracy of the information it provided in May 2009 in response to a request under 21 C.F.R. § 314.53(f). The FDA, however, has not requested any additional information nor has it requested any change to Novo Nordisk's new use

code narrative.

II. Novo Nordisk Amended The Use Code Narrative *After* Providing Notice To The FDA And FDA's Counsel

9. In late February 2009, Novo Nordisk instructed its outside regulatory counsel, Robert A. Dormer from Hyman, Phelps & McNamara, P.C., to meet with the FDA. Mr. Dormer and a colleague from his law firm met with four members of the FDA's Office of Chief Counsel. During the course of that meeting, the FDA asked about the use code for PRANDIN® in connection with a discussion concerning the new unitary indication required by the FDA as discussed above. *See* Declaration of Robert A. Dormer.

10. Following the meeting, Mr. Dormer advised us that he told the FDA members that the current use code no longer reflected the approved indication for PRANDIN®, and that Novo Nordisk was considering changing the use code to reflect the new approved indication. Mr. Dormer told us that none of the FDA members raised any objection or concern.

III. Novo Nordisk Amended The Use Code Narrative *After* Consultation With Outside Counsel

11. As a pharmaceutical company, Novo Nordisk takes its obligations to the FDA very seriously, and whenever questions arise as to proper FDA procedure, we are careful to retain highly-skilled FDA counsel and obtain their expertise and advice. We followed this procedure in connection with the change in our use code narrative for PRANDIN®, before filing Form 3542 in May 2009.

IV. Novo Nordisk Has Consistently Told The FDA That The '358 Patent Only Claims The Use Of Repaglinide In Combination With Metformin

12. In various submissions to the FDA, Novo Nordisk has consistently told the FDA that claim 4 of the '358 patent only claims the use of repaglinide in combination therapy with metformin.

13. For example, on June 9, 2008, Novo Nordisk expressly advised the FDA in writing that claim 4 of the '358 patent is limited to the use of repaglinide in combination therapy with metformin. *See* Novo Nordisk Citizen Petition, dated June 9, 2008, at 3 n.4 (Exhibit B) ("[T]he '358 patent contains 5 claims, one of which (claim 4) is directed to a method of treatment of NIDDM with a combination of repaglinide and metformin. The remaining claims of the '358 patent are directed towards either a pharmaceutical composition containing both repaglinide and metformin (claims 1-3) or to a kit comprised of at least repaglinide and metformin (claim 5).").

14. On December 4, 2008, the FDA acknowledged in writing that claim 4 of the '358 patent is limited to the use of repaglinide in combination therapy with metformin. *See* FDA Response to Citizen Petitions, dated December 4, 2008 (Exhibit C) ("The '358 patent expires on June 12, 2018, and claims, among other things, the use of repaglinide in combination with metformin. . . . [C]laim 4, the focus of these petitions, concerns the method of use for the combination of repaglinide and metformin in treating type 2 diabetes.").

15. Novo Nordisk has never told the FDA that the '358 patent claims the use of repaglinide in monotherapy or in combination therapy with thiazolidi-

nediones.

V. Novo Nordisk Has Consistently Maintained That Withholding Or "Carving Out" Information About The Predominant Approved Use Of Repaglinide Is Unsafe, Inadequate And Improper

16. Novo Nordisk also amended the use code narrative in May 2009 to prevent generic applicants from withholding critical information about the predominant approved use of repaglinide from consumers and health care practitioners.

17. On June 9, 2008, Novo Nordisk submitted a Citizen Petition requesting that the FDA refrain from approving any Abbreviated New Drug Application ("ANDA") for repaglinide that omits from its product label information about the approved use of repaglinide in combination with metformin. Nova Nordisk did *not* request the FDA to refrain from approving ANDAs for repaglinide that include in their product labels information about the approved use of repaglinide in combination with metformin. The predominant approved use of repaglinide is in combination therapy with metformin.

18. As Novo Nordisk stated in its Citizen Petition, omitting information about the predominant approved use of repaglinide from the labels of generic repaglinide products "would result in insufficient and misleading information being provided to physicians prescribing generic repaglinide, to pharmacists dispensing the drug, and to patients using the drug." Exhibit B at 1.

19. On July 14, 2008, Caraco filed a Citizen Petition requesting that the FDA approve ANDAs for repaglinide that contain a "split certification" with re-

spect to the '358 patent, so that information about the approved use of repaglinide in combination therapy with metformin could be omitted or "carved out" from labels for generic repaglinide products. Caraco Citizen Petition, dated July 14, 2008, at 2 (Exhibit D).

20. On December 4, 2008, the FDA issued a Response denying Novo Nordisk's Citizen Petition and granting Caraco's Citizen Petition. Novo Nordisk promptly filed a Petition for Reconsideration on, *inter alia,* the ground that "reconsideration would serve the public health since a generic repaglinide product with labeling that omits reference to the metformin combination use is less safe and effective . . ." Novo Nordisk accompanied that filing with a Petition to Stay, so that no generic applicant would be allowed to carve out this critical information before the FDA had an opportunity to consider the arguments in our Petition for Reconsideration. *See* Exhibits E and F.

21. As discussed above, our regulatory counsel met with the FDA in late February 2009. Once again, Novo Nordisk raised its concern that carving out information about the use of repaglinide in combination therapy with metformin was unsafe and ineffective.

22. Following the February 2009 meeting with regulatory counsel and the May 2009 submission of a new use code narrative, the FDA advised Novo Nordisk by phone that it would not permit Caraco or any other generic applicants to omit from their product label information regarding the approved use of repaglinide in combination with metformin.

23. On June 16, 2009, the FDA denied Novo

Nordisk's Petition for Reconsideration as moot "[b]ecause the use code for the '358 patent has changed since our issuance of the Citizen Petition Response and because our analysis and conclusions regarding labeling carveouts in that Citizen Petition Response were based on the previous use code." FDA Letter, dated June 16, 2009, at 3 (Exhibit G).

24. It is Novo Nordisk's understanding that Caraco and other ANDA applicants for generic repaglinide are required to include in their product labels data and information for doctors, pharmacists and patients regarding the predominant approved use of repaglinide.

I hereby declare under penalty of perjury that the foregoing is true and correct.

Executed this 10th day of September 2009 in Galloway, New Jersey.

/s/ James C. Shehan
James C. Shehan

* * * *

[Certificate of Service Omitted]

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

CONFIDENTIAL
SUBJECT TO PROTECTIVE ORDER

Civil Action No.: 2:05 CV 40188
Hon. Avern Cohn

DECLARATION OF DAVID L. ROSEN

FILED UNDER SEAL PURSUANT TO PROTECTIVE ORDER (DOCKET NO. 40)

I, David L. Rosen, hereby declare:

1. I am a resident of the state of Maryland. I respectfully submit this declaration in opposition to the Motion by Defendant Caraco Pharmaceutical Laboratories, Ltd. ("Caraco") for Summary Judgment on its Fourth Counterclaim and Sixth Affirmative Defense. I have personal knowledge of the facts set forth herein, and if called upon to testify, I could and would competently testify thereto.

I. SCOPE OF WORK

2. I have been retained as an expert witness by plaintiffs Novo Nordisk A/S and Novo Nordisk Inc. (collectively, "Novo Nordisk"). I have been asked to provide an independent expert opinion regarding the "use code" information submitted by Novo Nordisk to the Food and Drug Administration ("FDA") for publication in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (commonly referred to as FDA's "Orange Book"), based on my extensive experience and expertise with FDA regulatory issues (discussed below). A list of the materials that I have considered in forming my opinion is provided in Exhibit A.

II. QUALIFICATIONS

3. For 14 years (1978-1992), I was employed by the FDA, progressing to various supervisory positions involving virtually all aspects related to the drug approval process, combination products, jurisdictional issues and related compliance activities. I have significant experience in food and drug regulation, including a range of FDA regulatory issues affecting prescription and over-the-counter pharmaceuticals. My positions at FDA were in what is now known as the Center for Drug Evaluation and Research ("CDER"). My positions included the following: (a) Bureau of Drugs Lexicographer with responsibility for standardizing computerized drug information systems, including the design, format and data standardization and quality control for the first FDA Orange Book published in 1979; (b) Supervisory Consumer Safety Officer, in now what is known as the Office of Generic Drugs; (c) Consumer Safety Officer and Supervisory Consumer Safety Officer, Division of Anti-Viral Drug

Products; (d) Regulatory Counsel and Special Assistant to the Director of the Office of New Drug Evaluation; and (e) Regulatory Counsel and Special Assistant to the Director, CDER.

4. In 1979, I received the Commissioner's Special Citation for my work on the FDA's Orange Book and the Public Health Service Achievement Medal in 1981 for my work on the FDA's Orange Book and other FDA automated data bases. I have worked on Orange Book issues both inside and outside the FDA for over 30 years.

5. I have authored numerous published articles regarding FDA regulatory issues, including articles concerning the FDA's "Orange Book." My published articles include:

- "A Practical Guide to Drug Product Selection: Getting to Know the Food and Drug Administration's (FDA's) Approved Drug Products List (Orange Book) with Therapeutic Equivalence Evaluations," *Journal of Pharmacy Practice*, Vol. III, No. 3, June 1995

- "The Orange Book - Drug Product Equivalence and Pharmacist Liability," *Continuing Education Program for Pharmacists*, ABCOMM, Inc., 1997

- "Some Practical Advice on the Interchangeability of Levothyroxine Drug Products and Drug Product Selection," *Journal of Pharmacy Practice*, Vol. X, No. 5, October 1997

- "The Regulatory Affairs Professional and Device Reform," It's the Law Article, *Regulatory Affairs Focus*, Vol. 3, Issue 1, January 1998

- "Pharmacy Compounding: The State of the Art and the Law," It's the Law Article, *Regulatory Af-*

fairs Focus, Vol. 3, Issue 11, November 1998

- "Generic Drug Approval Process: Pre-1984 History Concerning Generic Drugs," *The Pharmaceutical Regulatory Process*, Vol. 144, 2005

6. I am a frequent speaker before national and international pharmaceutical industry associations on the Investigational New Drug exemption ("IND"), New Drug Application ("NDA"), and Abbreviated New Drug Application ("ANDA") submission and review process at the FDA.

7. I earned my Bachelor of Science degree in Pharmacy from the University of Connecticut School of Pharmacy in 1978, and my J.D. through the evening program at The Catholic University of America, Columbus School of Law in 1991. I am admitted to the bars of Washington, D.C. and Maryland.

8. I am currently a partner and co-chair of the Life Sciences Industry Team at Foley & Lardner LLP. I am the head of the FDA Practice at Foley & Lardner LLP. I am also a member of the firm's Public Affairs, and Corporate Compliance & Enforcement Practices and the Health Care, Nanotechnology and Food Industry Teams. I have previously also been a partner at three other law firms. I have represented both innovator and generic pharmaceutical companies, though the majority of my pharmaceutical work in private practice has been for generic pharmaceutical companies.

III. SUMMARY OF OPINIONS

9. The current U-968 use code for PRANDIN® is accurate and proper. The use code narrative accurately reflects the approved indication for PRANDIN®. There is nothing misleading or inaccurate about U-

968. It is entirely consistent with the use code narratives that FDA generated before August 18, 2003, as well as those use code narratives that NDA holders have proposed, and the FDA has published, since August 18, 2003.

10. Box 4.2b of FDA Form 3542 dictates exactly what the NDA holder must provide in terms of a use code narrative. The NDA holder is given the choice between the "approved indication or method of use" to utilize as its use code narrative. No other provision of FDA regulation or practice supersedes what Box 4.2b expressly provides.

11. While Caraco believes there may be an inconsistency between Box 4.2b and an instruction at the back of Form 3542, Box 4.2b does not require an NDA holder to define the scope of its patent claim. Rather, it directs NDA holders to provide a "description of the approved indication or method of use." Thus, use codes are based on a description of the indication or method of use approved by the FDA, not a description of the patent claims granted by the U.S. Patent and Trademark Office ("USPTO"). The U-968 use code narrative for PRANDIN® in the FDA's Orange Book tracks the indication in the FDA-approved label for PRANDIN® and it is both accurate and proper.

12. Based on my review of the materials that Caraco submitted to the FDA, the FDA has rejected Caraco's interpretation of what Box 4.2b of Form 3542 requires. Instead, the FDA has published Novo Nordisk's proposed use code narrative over Caraco's objections, and instructed Caraco to conform its patent certification to Novo Nordisk's new use code.

IV. THE FDA FORMS FOR SUBMITTING PATENT RELATED INFORMATION

13. When a new drug application is submitted to FDA and is undergoing rigorous FDA review, an NDA applicant is required to submit FDA Form **3542a**, with information regarding any patents it has that claim the drug or a method of using the drug being reviewed. A copy of FDA Form 3542a is attached hereto as Exhibit B. When the NDA is approved, the NDA holder must then submit FDA Form **3542**. A copy of FDA Form 3542 is attached hereto as Exhibit C.

14. The FDA is the author and creator of these forms. From time to time, the FDA amends the forms to require new or additional information. The FDA decides what goes into the form. The forms have an expiration date and applicants are required to use a form that is within the expiration date. The forms are subject to review and approval by the Office of Management and Budget.

15. Form 3542a does *not* ask for "use code" descriptions, whereas Form 3542 does request such information in Box 4.2b. The reason that Form 3542a does not ask for use code descriptions is because the applicant must have an *approved* label before it can provide the description required for the use code. Even though the patent exists when the NDA applicant files Form 3542a, the NDA applicant does not know what the approved indication or approved method of use will be prior to the FDA approving the application.

16. On Form 3542, there are two distinct narrative questions that ask the NDA holder different information concerning its method of use patent —

Boxes 4.2a and 4.2b. Box 4.2a asks an NDA holder to identify the portions of the approved label that refer to the approved method of use *claimed by the patent.* This is where the NDA holder correlates the claims of its method patent to the approved label. In contrast, Box 4.2b asks the NDA holder to propose a use code narrative based on a "description of the approved indication or method of use." Box 4.2b does *not* ask an NDA holder to define the scope of its patent, or provide an analysis of any patent claim. The answer to Box 4.2b (*i.e.*, the use code narrative) does not depend on the scope of the patent claim.

V. BACKGROUND FACTS CONCERNING PRANDIN®

17. In 1997, Novo Nordisk submitted an NDA to sell repaglinide in the U.S. under the brand name PRANDIN®. In 1997, the FDA approved PRANDIN® for use in the treatment of type 2 diabetes as a monotherapy and as a combination therapy with metformin. I am advised that the predominant approved use of PRANDIN® is in combination therapy with metformin. When the FDA approved Novo Nordisk's NDA in 1997, Novo Nordisk held U.S. Patent No. 5,312,924 (the "'924 patent"), which claimed a method of using repaglinide.

18. In 1997, the FDA created and published the following use code for the '924 patent in the Orange Book: "U-214 – Use as a blood glucose-lowering agent." U-214 tracked the approved indication for PRANDIN® which read in relevant part: "PRANDIN is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with type 2 diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled satisfactorily by diet and exercise alone."

When the FDA created U-214, there were two approved uses for PRANDIN®. The '924 patent contained a method of use claim directed only to the use of repaglinide in monotherapy. A copy of the Orange Book entry for PRANDIN® in 1997 is attached hereto as Exhibit D.

19. Currently, Novo Nordisk holds U.S. Patent No. 6,677,358 (the "'358 patent"), a patent that was issued by the USPTO in January 2004. The '358 patent claims an approved method of using the drug. Claim 4 of the '358 patent covers "[a] method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin."

20. In 2004, the "Indications and Usage" section of the FDA-approved label for PRANDIN® contained a separate indication for FDA-approved uses of repaglinide in combination therapy: "PRANDIN is also indicated for combination therapy use (with metformin or thiazolidinediones) to lower blood glucose in patients whose hyperglycemia could not be controlled by diet and exercise, plus monotherapy with metformin, sulfonylureas, repaglinide, or thiazolidinediones." A copy of the FDA-approved PRANDIN® label from 2004 is attached hereto as Exhibit E.

21. In November 2007, the FDA decided that separate indications of usage for PRANDIN® – whether for monotherapy or combination therapy –should be eliminated and that a single approved indication should appear as follows:

Under **INDICATIONS AND USAGE**

Replace all the separate indications (e.g., monotherapy, combination therapy, and initial or

second-line therapy) with the following sentence:

"Prandin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus."

See Exhibit F.

22. Novo Nordisk changed its label, and the FDA approved the new PRANDIN® label in July 2008. The "Indications and Usage" section of the FDA-approved label now states that "PRANDIN is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus." A copy of the current FDA-approved label for PRANDIN® is attached hereto as Exhibit G. In May 2009, Novo Nordisk submitted to the FDA a proposed amended use code description for PRANDIN® on FDA Form 3542. A copy of Novo Nordisk's submission is attached hereto as Exhibit H. The proposed amended use code description for PRANDIN® tracked the new approved indication for PRANDIN®: "A method for improving glycemic control in adults with type 2 diabetes mellitus."

23. The FDA assigned use code U-968 to the proposed amended use code description for PRANDIN® and published the U-968 use code and description in the Orange Book.

VI. OPINIONS

24. Based on my review of the material set forth in Exhibit A and my extensive experience with FDA regulatory issues, including my 14 years at the FDA, it is my professional opinion that the information submitted by Novo Nordisk in May 2009 on FDA

Form 3542 and the current use code for PRANDIN® in the FDA's Orange Book are accurate.

A. Novo Nordisk's May 2009 Submission Is Accurate

25. In its May 2009 submission on Form 3542, Novo Nordisk accurately identified the specific claim number of the '358 patent that claims an approved use of PRANDIN®. In Box 4.2 of its May 2009 submission on Form 3542, Novo Nordisk accurately identified "Claim 4" as the specific claim of the '358 patent covering an approved use of PRANDIN® and accurately checked "Yes" in response to the question "Does (Do) the patent claim(s) referenced in 4.2 claim an approved method of use of the approved drug product" Exhibit H at 2.

26. Novo Nordisk provided accurate "use code" information for PRANDIN®. Novo Nordisk did exactly what the FDA requires by providing in Box 4.2b a description that directly tracks the approved indication of the new label for PRANDIN®: "A method for improving glycemic control in adults with type 2 diabetes mellitus." *Id.* at 3. *Compare with* Exhibit G ("PRANDIN is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus."). Providing the approved indication is both proper and accurate.

27. The approved indication has been used for use codes ever since the FDA created use codes in 1987. Indeed, the FDA has explained that "for a use patent, FDA includes in the Orange Book a code identifying ***the indication*** covered by the patent." 59 Fed. Reg. 50338, 50346 (Oct. 3, 1994) (emphasis added). The practice of providing the approved indication for the use code is well established and well accepted.

28. NDA holders routinely submit their approved indication as their use code narrative. For example, a review of the most recent use codes submitted by NDA holders (U-947 to U-997) shows that more than 30 out of the last 50 use code narratives describe the approved indication of the drug products marketed by the NDA holders. *See* U-947; U-948; U-949; U-950; U-951; U-954; U-956; U-964; U-965; U-966; U-967; U-968; U-969; U-970; U-971; U-972; U-973; U-974; U-975; U-976; U-977; U-978; U-979; U-980; U-981; U-983; U-984; U-985; U-986; U-987; U-989; U-992; U-996; U-997.

29. There is absolutely nothing wrong or improper about submitting the approved indication as the use code. That is exactly what Box 4.2b asks an NDA holder to provide. Alternatively, the NDA holder may provide the approved method of use, but either is proper. There is no FDA rule or precedent requiring one over the other.

30. Had I been engaged to provide counsel to Novo Nordisk with regard to its May 2009 submission, I would have advised Novo Nordisk that it was proper and accurate to provide the approved indication for PRANDIN® in Box 4.2b as its use code narrative, just like it did.

B. The Use Code For PRANDIN® Is Not Wrong Or Misleading As Caraco Contends

31. I understand that Caraco contends that the use code narrative for PRANDIN® proposed by Novo Nordisk and published by the FDA must be "corrected" because it "suggest[s] that the '358 patent covers all approved methods of using repaglinide (including montherapy and combination with TZDs)."

Caraco Third Amended Answer and Counterclaim, dated July 11, 2009, ¶ 100 (Dkt. 309).

32. Caraco's contention makes no sense. *First*, a use code narrative does not define or interpret the scope or coverage of a patent claim. As discussed above, Box 4.2b does not request or require any information concerning the scope or coverage of the patent claim. *Second*, Novo Nordisk's use code narrative refers only to a single method of using PRANDIN®: "***A method*** for improving glycemic control in adults with type 2 diabetes mellitus." Exhibit H at 3. (emphasis added).

33. Use codes serve the limited purpose of notifying ANDA applicants of "the existence of a patent that claims an approved use of a drug" and "are not meant to substitute for the applicant's review of the patent and the approved labeling." 68 Fed. Reg. 36676, 36683 (June 18, 2003).

34. The U-214 use code created by the FDA for PRANDIN® underscores the limited purpose of use codes. When the FDA created the U-214 use code for the '924 patent in 1997, there were two approved uses for PRANDIN®: use in monotherapy and use in combination therapy with metformin. The U-214 use code did not distinguish between the two approved uses, nor did it define the scope of the '924 patent. Rather, the U-214 use code described an approved use of PRANDIN®: "Use as a blood glucose-lowering agent."

35. The U-214 and U-968 use codes for PRANDIN® are similar to the use codes for other anti-diabetic drug products. The U-412 use code narrative for U.S. Patent No. 6,303,146 (the "'146 patent") is a good example. Like PRANDIN®, Bristol-Myers Squibb Company's product, GLUCOVANCE®, con-

tains a single approved indication: "GLUCOVANCE (Glyburide and Metformin HCl) Tablets is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus." Like PRANDIN®, GLUCOVANCE® has more than one approved use, including its use in combination therapy with TZDs. The U-412 use code does not distinguish between the approved uses, nor does it define the scope of the '146 patent. Rather, like the U-968 use code, the U-412 use code describes the approved indication of the drug: "U-412 – Treatment of type 2 diabetes." A copy of the GLUCOVANCE® label is attached hereto as Exhibit I.

36. The U-827 use code narrative created by Novartis for U.S. Patent No. 6,559,188 (the "'188 patent") is another good example. Like PRANDIN®, Novartis' product, Starlix®, contains a single approved indication: "Starlix® (nateglinide) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus." Like PRANDIN®, Starlix® has more than one approved use, including its use in combination therapy with metformin. The U-827 use code does not distinguish between the approved uses, nor does it define the scope of the '188 patent. Rather, like the U-968 use code, the U-827 use code describes the approved indication of the drug: "U-827 – Use for treatment of diabetes, particularly type 2 diabetes." A copy of the Starlix® label is attached hereto as Exhibit J.

37. Other use codes in the Orange Book similarly illustrate that use codes serve a limited purpose and are not meant to define the scope of a patent claim:

U-55 – Treatment of pain

U-111 – Diabetes

U-118 – Method of lowering blood sugar level

U-185 – Method of treating hypertension

U-228 – Asthma

U-279 – Method of use of the approved product

U-305 – Methods for using the drug product

U-533 – Erectile dysfunction

U-621 – Method of treating cancer

U-669 – Indication of type II diabetes

U-752 – Sunscreen

U-780 – A method for the treatment of cancer

U-801 – Method of treating cancer

U-851 – Treatment of type 2 diabetes mellitus

U-860 – For the approved uses and conditions of use, including depression

U-952 – Use as an analgesic

U-976 – Improvement of glycemic control in individuals with type 2 diabetes.

A list of the "use codes" that have been published in the FDA's Orange Book as of the date of this declaration is attached hereto as Exhibit K.

38. The use code for PRANDIN® in the FDA's Orange Book is proper and accurate. It tracks the approved indication for PRANDIN®, alerts ANDA applicants to the existence of the '358 patent and provides notice that the '358 patent claims "a method [of using PRANDIN®] for improving glycemic control in adults with type 2 diabetes mellitus."

39. In this case, given that the FDA eliminated all of the separate indications for PRANDIN® and

created a new unitary indication, I would have advised Novo Nordisk to do exactly what it did; namely, change its use code narrative to match the new approved indication.

40. I also understand that Caraco contends Novo Nordisk's change in use code narrative was untimely. But there is no time limitation that applies to changes in use code narratives. The 30-day period to which Caraco refers relates only to the listing of new patents or changes in expiration dates.

C. The FDA Has Accepted And Published Novo Nordisk's New Use Code For PRANDIN®

41. The FDA has effectively confirmed the propriety of the use code narrative for PRANDIN®.

42. In a June 9, 2008 submission, Novo Nordisk represented to the FDA that "the '358 patent contains 5 claims, one of which (claim 4) is directed to a method of treatment of NIDDM with a combination of repaglinide and metformin." A copy of Novo Nordisk's submission is attached hereto as Exhibit L.

43. In a December 4, 2008 response to Novo Nordisk, the FDA stated: "The '358 patent expires on June 12, 2018, and claims, among other things, the use of repaglinide in combination with metformin. . . .

[C]laim 4, the focus of these petitions, concerns the method of use for the combination of repaglinide and metformin in treating type 2 diabetes." A copy of the FDA's response is attached hereto as Exhibit M.

44. Thus, when Novo Nordisk proposed the amended use code for PRANDIN® in its May 2009 submission on Form 3542, the FDA was aware of the scope of claim 4 of the '358 patent.

45. Box 4.2b of Form 3542 asks an NDA holder to "propose" a use code: "Submit the description of the approved indication or method of use that you ***propose*** FDA include as the 'Use Code' in the Orange Book." Exhibit C at 3 (emphasis added). Directly below Box 4.2b, the FDA warns that it "will not list the patent in the Orange Book as claiming the method of use if . . . the information requested in . . . 4.2b is not provided in full." *Id.*

46. Accordingly, if the FDA thought that the use code narrative that Novo Nordisk provided in Box 4.2b was incomplete or improper, the FDA would not have assigned use code U-968 to Novo Nordisk's proposed narrative and published the U-968 use code and narrative in the Orange Book. On the contrary, the FDA never raised any question concerning the new use code narrative.

D. The FDA Has Rejected Caraco's Objections To The Use Code For PRANDIN®

47. On May 29, 2009, Caraco sent the FDA a letter asserting that Novo Nordisk's use code change was untimely. A copy of Caraco's letter to the FDA is attached hereto as Exhibit N.

48. On June 1, 2009, Caraco sent the FDA a letter "to request correction of an erroneous Orange Book submission by Novo Nordisk." Caraco asserted that the amended use code for PRANDIN® violated the FDA's regulations and requested that the FDA change the use code for PRANDIN® back to the old use code:

> Novo has impermissibly broadened the description of the Prandin use code far beyond the scope of the only applicable method patent claim . . .

> Novo's new use code does not purport to describe the patented method itself and arguably could be construed as vaguely suggesting that the patent covers other approved *but unprotected* uses of repaglinide, including monotherapy and combination therapy with thiazolidnediones (TZDs).
>
> Novo's use code change is manifestly improper and conflicts with the rules set forth in Section 314.53. It should be corrected without delay. . .
>
> .
>
> FDA has powers – and responsibilities – just the same. Pursuant to 21 C.F.R. § 314.53 (f), we request that the Prandin use code for U.S. Patent No. 6,677,358 be restored to the original, and accurate, description: use of repaglinide in combination with metformin to lower blood glucose.

(Emphasis in original). A copy of Caraco's letter to the FDA is attached hereto as Exhibit O.

49. The FDA did not grant Caraco its requested relief. Instead, as Caraco admits, "on June 16, 2009, FDA issued a ruling . . . confirming that it has accepted Novo's use code change." Caraco's Brief in Support of Motion for Summary Judgment, dated June 19, 2009, at 8 (Dkt. 317).

50. It appears from the documents I have reviewed, all of the arguments that Caraco has made in this proceeding, it has made to the FDA. The FDA knows what is required by Form 3542 and the FDA knows what is required for an adequate use code. The FDA has rejected each of Caraco's arguments, and, on August 3, 2009, asked Caraco to conform its patent certification to Novo Nordisk's new use code. A copy

of an August 3, 2009 facsimile from the FDA to Caraco is attached hereto as Exhibit P.

E. Box 4.2b Of Form 3542 Expressly Permits An NDA Holder To Propose "A Description Of The Approved Indication" As The Use Code

51. By objecting to Novo Nordisk's use code narrative, Caraco essentially seeks to read out of Box 4.2b of Form 3542 the express option for NDA holders to provide a "description of the approved indication."

52. Caraco contends that the description of the approved indication that Novo Nordisk provided in Box 4.2b on Form 3542 "conflicts" with FDA regulations in 21 C.F.R. § 314.53 (Exhibit O at 2), but ignores that FDA regulations contemplate the submission of "a description of each approved method of use ***or indication***" in the approved label of a drug product. 21 C.F.R. § 314.53(c)(2)(ii)(P)(1) (emphasis added). Similarly, in the Federal Register, the FDA has explained that "for a use patent, FDA includes in the Orange Book a code identifying ***the indication*** covered by the patent." 59 Fed. Reg. at 50346 (emphasis added).

53. Caraco relies on a provision in 21 C.F.R. § 314.53 calling for "[t]he description of the patented method of use as required for publication." 21 C.F.R. § 314.53(c)(2)(ii)(P)(3). At most, Caraco has identified an ambiguity in the FDA regulations, but a perceived ambiguity in FDA regulations is not a basis for reading out of Box 4.2b of Form 3542 the express option for NDA holders to provide a "description of the approved indication."

54. Caraco also attempts to rely on the separate page entitled "Information and Instructions" at the

back of Form 3542. In particular, Caraco relies on a sentence which states: "Each approved use claimed by the patent should be separately identified in this section and contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method of use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval." Exhibit C at 4.

55. Caraco ignores the immediately preceding sentence, which reiterates that a NDA holder may use either the approved indication or method of use: "The use code designates a method of use patent that claims the approved indication or use of a drug product." *Id.* At most, Caraco has identified an ambiguity or inconsistency between Box 4.2b and the separate information at the back of the form. The general information at the back of the form does not override the express directions in Box 4.2b. Moreover, this instruction does not render meaningless the multitude of use codes created by FDA and by NDA holders alike, which are drawn and directed to the approved indication.

56. The FDA is authorized to interpret its own regulations, as it did in creating Form 3542, which was approved by the Office of Management and Budget (Exhibit C at 1), and only the FDA can change what Box 4.2b requires. Any perceived ambiguities or inconsistencies in Box 4.2b of Form 3542 and other FDA requirements should be brought to the attention of the FDA. The FDA regulations and instructions that Caraco relies on do not supersede what is required on Form 3542. The boxes on the forms control what NDA holders are required to provide to the FDA.

I hereby declare under penalty of perjury that the foregoing is true and correct.

Executed this 10th day of September 2009 in Washington, D.C.

/s/ David L. Rosen
David L. Rosen

* * * *

[Certificate of Service Omitted]

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

Civil Action No.: 2:05 CV 40188
Hon. Avern Cohn

EXHIBIT A TO THE DECLARATION OF DAVID L. ROSEN

1. FDA Form 3542a.

2. FDA Form 3542.

3. FDA Orange Book.

4. List of use codes that have been published in the FDA Orange Book, as available at http://www.accessdata.fda.gov/scripts/cder/ob/docs/patternsall.cfm.

5. U.S. Patent 5,312,924.

6. FDA Orange Book entry for PRANDIN® in December 1997.

7. U.S. Patent 6,677,358.

8. PRANDIN® label from 2004.

9. Novo Nordisk submission on Form 3542,

dated February 5, 2004.

10. FDA Orange Book entry for PRANDIN® in December 2004.

11. FDA Letter to Novo Nordisk, dated November 21, 2007.

12. Novo Nordisk Citizen Petition, dated June 9, 2008.

13. FDA Response to Citizen Petitions, dated December 4, 2008.

14. Novo Nordisk submission on Form 3542, dated May 6, 2009.

15. Caraco Letter to FDA, dated May 29, 2009.

16. Caraco Letter to FDA, dated June 1, 2009.

17. Caraco Third Amended Answer and Counterclaim, dated July 11, 2009.

18. FDA Response to Novo Nordisk Petition for Reconsideration, dated June 16, 2009.

19. Caraco Brief in Support of Motion for Summary Judgment, dated June 19, 2009.

20. FDA facsimile to Caraco, dated August 3, 2009.

21. Current PRANDIN® label.

22. Current FDA Orange Book entry for PRANDIN®.

23. GLUCOVANCE® label.

24. U.S. Patent 6,303,146.

25. Starlix® label.

26. U.S. Patent 6,559,188.

27. Indications for drug products associated with use codes U-947 to U-997.

UNITED STATES DISTRICT COURT
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Defendants-Counterclaim Plaintiffs.

Civil Action No.: 2:05 CV 40188
Hon. Avern Cohn

EXHIBIT B TO THE DECLARATION OF DAVID L. ROSEN

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 3.

NDA NUMBER

NAME OF APPLICANT/NDA HOLDER

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ACTIVE INGREDIENT(S)

STRENGTH(S)

DOSAGE FORM

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA, application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

[illegible]

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent

d. Name of Patent Owner	Address (of Patent Owner)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	☐ Yes	☐ No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	☐ Yes	☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2 Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3 Drug Product (Formulation or Composition)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4 Method(s) of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2 Patent Claim Number(s) *(as listed in the patent)* — **Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?**	☐ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. — Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*		

5 No Relevant Patents

For the pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6 Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name	
Address	City/State
ZIP Code	Telephone Number
FAX Number *(if available)*	E-Mail Address *(if available)*

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer (HFA-710)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

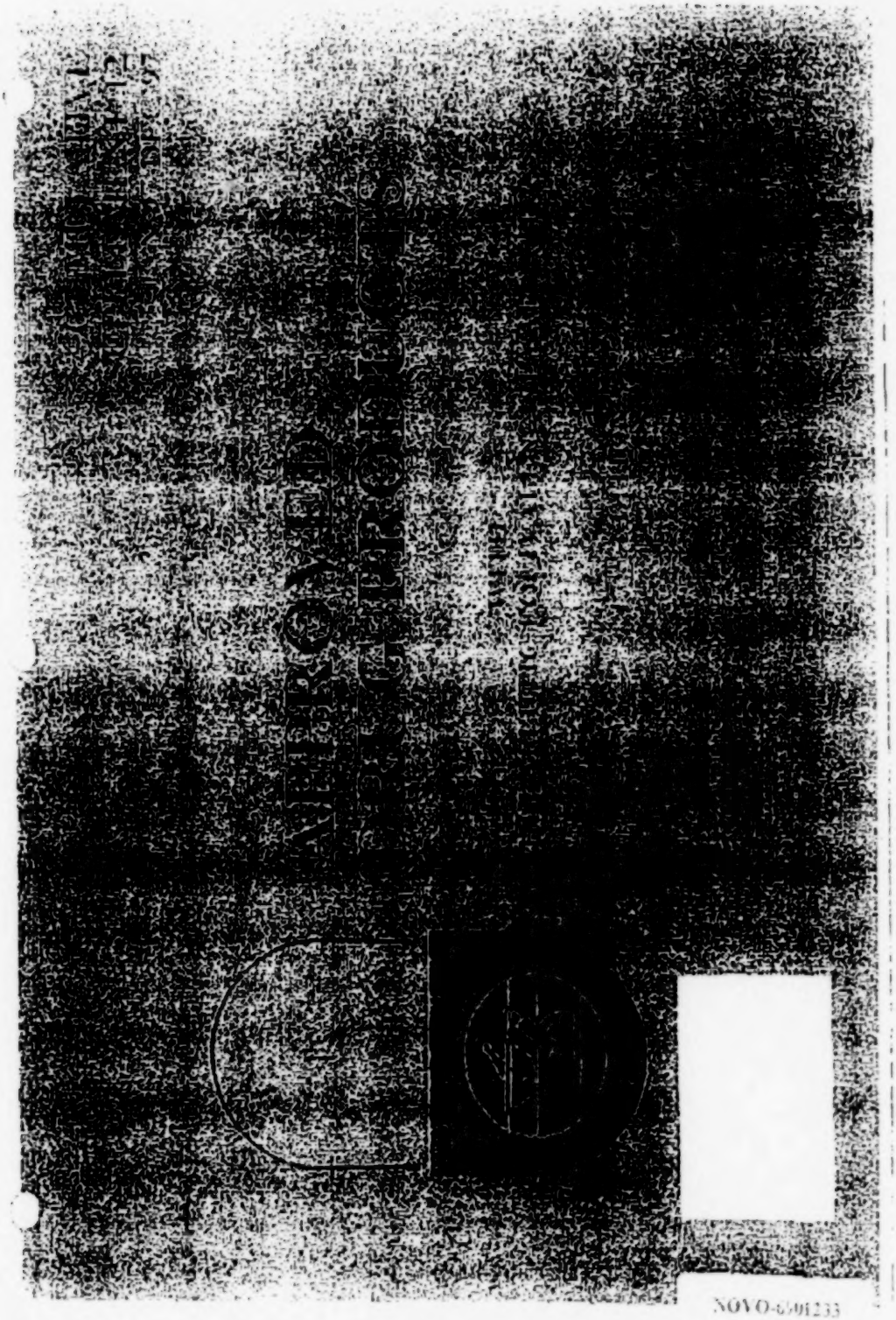
Civil Action No.: 2:05 CV 40188
Hon. Avern Cohn

EXHIBIT C TO THE DECLARATION OF DAVID L. ROSEN

* * * *

[Exhibit C Reproduced at Pet. App. 211a - 214a]

144



NOVO-6901233

PATENT AND EXCLUSIVITY TERMS
PATENT USE CODE

U-210	METHOD OF TREATING CONGESTIVE HEART FAILURE
U-211	USE IN PATIENTS WITH REVERSIBLE AIRWAY OBSTRUCTION
U-212	METHOD OF TREATMENT OF PARKINSON'S DISEASE
U-213	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING HYPERCHOLESTEROLEMIA AND METHOD FOR TREATING HYPERLIPIDEMIA
U-214	USE AS A BLOOD GLUCOSE-LOWERING AGENT

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

Civil Action No.: 2:05 CV 40188
Hon. Avern Cohn

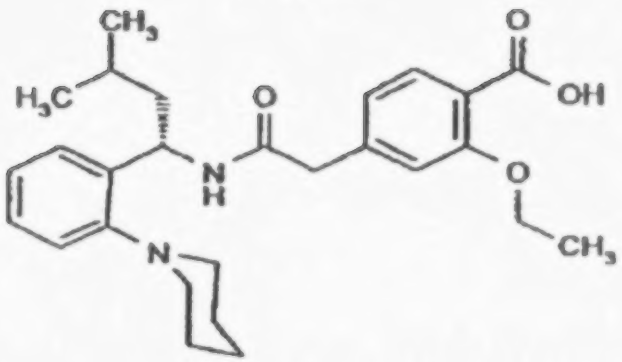
EXHIBIT E TO THE DECLARATION OF DAVID L. ROSEN

PRANDIN®
(repaglinide) Tablets (0.5, 1, and 2 mg)
Rx only

DESCRIPTION

PRANDIN® (repaglinide) is an oral blood glucose-lowering drug of the meglitinide class used in the management of type 2 diabetes mellitus (also known as non-insulin dependent diabetes mellitus or NIDDM). Repaglinide, S(+)2-ethoxy-4(2((3-methyl-1-(2-(1-piperidinyl) phenyl)- butyl) amino)-2-oxoethyl) benzoic acid, is chemically unrelated to the oral sulfonylurea insulin secretagogues.

The structural formula is as shown below:



Repaglinide is a white to off-white powder with molecular formula C_{27} H_{36} N_2 O_4 and a molecular weight of 452.6. PRANDIN tablets contain 0.5 mg, 1 mg, or 2 mg of repaglinide. In addition each tablet contains the following inactive ingredients: calcium hydrogen phosphate (anhydrous), microcrystalline cellulose, maize starch, polacrilin potassium, povidone, glycerol (85%), magnesium stearate, meglumine, and poloxamer. The 1 mg and 2 mg tablets contain iron oxides (yellow and red, respectively) as coloring agents.

CLINICAL PHARMACOLOGY

Mechanism of Action

Repaglinide lowers blood glucose levels by stimulating the release of insulin from the pancreas. This action is dependent upon functioning beta (ß) cells in the pancreatic islets. Insulin release is glucose-dependent and diminishes at low glucose concentrations.

Repaglinide closes ATP-dependent potassium channels in the ß-cell membrane by binding at characterizable sites. This potassium channel blockade depolarizes the ß-cell, which leads to an opening of calcium channels. The resulting increased calcium influx induces insulin secretion. The ion channel mechanism is highly tissue selective with low affinity for heart and skeletal muscle.

Pharmacokinetics

Absorption: After oral administration, repaglinide is rapidly and completely absorbed from the gastrointestinal tract. After single and multiple oral doses in healthy subjects or in patients, peak plasma drug levels (C_{max}) occur within 1 hour (T_{max}). Repaglinide is rapidly eliminated from the blood stream with a half-life of approximately 1 hour. The mean absolute bioavailability is 56%. When repaglinide was given with food, the mean T_{max} was not changed, but the mean C_{max} and AUC (area under the time/plasma concentration curve) were decreased 20% and 12.4%, respectively.

Distribution: After intravenous (IV) dosing in healthy subjects, the volume of distribution at steady state (V_{ss}) was 31 L, and the total body clearance (CL) was 38 L/h. Protein binding and binding to human serum albumin was greater than 98%.

Metabolism: Repaglinide is completely metabolized by oxidative biotransformation and direct conjugation with glucuronic acid after either an IV or oral dose. The major metabolites are an oxidized dicarboxylic acid (M2), the aromatic amine (M1), and the acyl glucuronide (M7). The cytochrome P-450 enzyme system, specifically 3A4, has been shown to be involved in the N-dealkylation of repaglinide to M2 and the further oxidation to M1. Metabolites do not contribute to the glucose-lowering effect of repaglinide.

Excretion: Within 96 hours after dosing with ^{14}C-repaglinide as a single, oral dose, approximately 90% of the radiolabel was recovered in the feces and approximately 8% in the urine. Only 0.1% of the dose is cleared in the urine as parent compound. The major metabolite (M2) accounted for 60% of the adminis-

tered dose. Less than 2% of parent drug was recovered in feces.

Pharmacokinetic Parameters: The pharmacokinetic parameters of repaglinide obtained from a single-dose, crossover study in healthy subjects and from a multiple-dose, parallel, dose-proportionality (0.5, 1, 2 and 4 mg) study in patients with type 2 diabetes are summarized in the following table:

Parameter	Patients with type 2 diabetes[a]
Dose 0.5 mg 1 mg 2 mg 4 mg	$AUC_{0\text{-}24\ hr}$ Mean±SD (ng/mL*hr): 68.9 ± 154.4 125.8 ± 129.8 152.4 ± 89.6 447.4 ± 211.3
Dose 0.5 mg 1 mg 2 mg 4 mg	$C_{max0\text{-}5\ hr}$ Mean ±SD (ng/mL): 9.8 ± 10.2 18.3 ± 9.1 26.0 ± 13.0 65.8 ± 30.1
Dose 0.5 - 4 mg	$T_{max0\text{-}5\ hr}$ Means (SD) 1.0 - 1.4 (0.3 - 0.5) hr
Dose 0.5 - 4 mg	$T_{1/2}$ Means (Ind Range) 1.0 - 1.4 (0.4 - 8.0) hr
Parameter	**Healthy Subjects**
CL based on i.v.	38 ± 16 L/hr
V_{ss} based on i.v.	31 ± 12 L
AbsBio	56 ± 9%

a: dosed preprandially with three meals

CL = total body clearance
V_{ss} = volume of distribution at steady state
AbsBio = absolute bioavailability

These data indicate that repaglinide did not accumulate in serum. Clearance of oral repaglinide did not change over the 0.5 - 4 mg dose range, indicating a linear relationship between dose and plasma drug levels.

Variability of Exposure: Repaglinide AUC after multiple doses of 0.25 to 4 mg with each meal varies over a wide range. The intra-individual and inter-individual coefficients of variation were 36% and 69%, respectively. AUC over the therapeutic dose range included 69 to 1005 ng/mL*hr, but AUC exposure up to 5417 ng/mL*hr was reached in dose escalation studies without apparent adverse consequences.

Special Populations:

Geriatric. Healthy volunteers were treated with a regimen of 2 mg taken before each of 3 meals. There were no significant differences in repaglinide pharmacokinetics between the group of patients <65 years of age and a comparably sized group of patients ≥65 years of age. (See **PRECAUTIONS, Geriatric Use)**

Pediatric. No studies have been performed in pediatric patients.

Gender. A comparison of pharmacokinetics in males and females showed the AUC over the 0.5 mg to 4 mg dose range to be 15% to 70% higher in females with type 2 diabetes. This difference was not reflected in the frequency of hypoglycemic episodes (male: 16%; female: 17%) or other adverse events. With respect to gender, no change in general dosage recommendation is indicated since dosage for each patient should be indivi-

dualized to achieve optimal clinical response.

Race. No pharmacokinetic studies to assess the effects of race have been performed, but in a U.S. 1-year study in patients with type 2 diabetes, the blood glucose-lowering effect was comparable between Caucasians (n=297) and African-Americans (n=33). In a U.S. dose-response study, there was no apparent difference in exposure (AUC) between Caucasians (n=74) and Hispanics (n=33).

Drug-Drug Interactions:

Drug interaction studies performed in healthy volunteers show that PRANDIN had no clinically relevant effect on the pharmacokinetic properties of digoxin, theophylline, or warfarin. Co-administration of cimetidine with PRANDIN did not significantly alter the absorption and disposition of repaglinide.

Additionally, the following drugs were studied in healthy volunteers with co-administration of PRANDIN. Listed below are the results:

Gemfibrozil and Itraconazole: Co-administration of gemfibrozil (600 mg) and a single dose of 0.25 mg PRANDIN (after 3 days of twice-daily 600 mg gemfibrozil) resulted in an 8.1-fold higher repaglinide AUC and prolonged repaglinide half-life from 1.3 to 3.7 hr. Co-administration with itraconazole and a single dose of 0.25 mg PRANDIN (on the third day of a regimen of 200 mg initial dose, twice-daily 100 mg itraconazole) resulted in a 1.4-fold higher repaglinide AUC. Co-administration of both gemfibrozil and itraconazole with PRANDIN resulted in a 19-fold higher repaglinide AUC and prolonged repaglinide half-life to 6.1 hr. Plasma repaglinide concentration at 7 h increased 28.6-fold with gemfibrozil co-administration and 70.4-fold with the gemfibrozil-itraconazole combina-

tion (see **PRECAUTIONS, Drug-Drug Interactions**).

Ketoconazole: Co-administration of 200 mg ketoconazole and a single dose of 2 mg PRANDIN (after 4 days of once daily ketoconazole 200 mg) resulted in a 15% and 16% increase in repaglinide AUC and C_{max}, respectively. The increases were from 20.2 ng/mL to 23.5 ng/mL for C_{max} and from 38.9 ng/mL*hr to 44.9 ng/mL*hr for AUC.

Rifampin: Co-administration of 600 mg rifampin and a single dose of 4 mg PRANDIN (after 6 days of once daily rifampin 600 mg) resulted in a 32% and 26% decrease in repaglinide AUC and C_{max}, respectively. The decreases were from 40.4 ng/mL to 29.7 ng/mL for C_{max} and from 56.8 ng/mL*hr to 38.7 ng/mL*hr for AUC.

Levonorgestrel & Ethinyl Estradiol: Co-administration of a combination tablet of 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol administered once daily for 21 days with 2 mg PRANDIN administered three times daily (days 1-4) and a single dose on Day 5 resulted in 20% increases in repaglinide, levonorgestrel, and ethinyl estradiol C_{max}. The increase in repaglinide C_{max} was from 40.5 ng/mL to 47.4 ng/mL. Ethinyl estradiol AUC parameters were increased by 20%, while repaglinide and levonorgestrel AUC values remained unchanged.

Simvastatin: Co-administration of 20 mg simvastatin and a single dose of 2 mg PRANDIN (after 4 days of once daily simvastatin 20 mg and three times daily PRANDIN 2 mg) resulted in a 26% increase in repaglinide C_{max} from 23.6 ng/mL to 29.7 ng/mL. AUC was unchanged.

Nifedipine: Co-administration of 10 mg nifedipine with a single dose of 2 mg PRANDIN (after 4 days of

three times daily nifedipine 10 mg and three times daily PRANDIN 2 mg) resulted in unchanged AUC and C_{max} values for both drugs.

Clarithromycin: Co-administration of 250 mg clarithromycin and a single dose of 0.25 mg PRANDIN (after 4 days of twice daily clarithromycin 250 mg) resulted in a 40% and 67% increase in repaglinide AUC and C_{max}, respectively. The increase in AUC was from 5.3 ng/mL*hr to 7.5 ng/mL*hr and the increase in C_{max} was from 4.4 ng/mL to 7.3 ng/mL.

Renal Insufficiency. Single-dose and steady-state pharmacokinetics of repaglinide were compared between patients with type 2 diabetes and normal renal function (CrCl > 80 mL/min), mild to moderate renal function impairment (CrCl = 40 – 80 mL/min), and severe renal function impairment (CrCl = 20 – 40 mL/min). Both AUC and C_{max} of repaglinide were similar in patients with normal and mild to moderately impaired renal function (mean values 56.7 ng/mL*hr vs 57.2 ng/mL*hr and 37.5 ng/mL vs 37.7 ng/mL, respectively.) Patients with severely reduced renal function had elevated mean AUC and C_{max} values (98.0 ng/mL*hr and 50.7 ng/mL, respectively), but this study showed only a weak correlation between repaglinide levels and creatinine clearance. Initial dose adjustment does not appear to be necessary for patients with mild to moderate renal dysfunction. **However, patients with type 2 diabetes who have *severe* renal function impairment should initiate PRANDIN therapy with the 0.5 mg dose – subsequently, patients should be carefully titrated. Studies were not conducted in patients with creatinine clearances below 20 mL/min or patients with renal failure requiring hemodialysis.**

Hepatic Insufficiency. A single-dose, open-label study was conducted in 12 healthy subjects and 12 patients with chronic liver disease (CLD) classified by Child-Pugh scale and caffeine clearance. Patients with moderate to severe impairment of liver function had higher and more prolonged serum concentrations of both total and unbound repaglinide than healthy subjects ($AUC_{healthy}$: 91.6 ng/mL*hr; $AUC_{CLD\ patients}$: 368.9 ng/mL*hr; $C_{max,\ healthy}$: 46.7 ng/mL; $C_{max,\ CLD\ patients}$: 105.4 ng/mL). AUC was statistically correlated with caffeine clearance. No difference in glucose profiles was observed across patient groups. Patients with impaired liver function may be exposed to higher concentrations of repaglinide and its associated metabolites than would patients with normal liver function receiving usual doses. Therefore, **PRANDIN should be used cautiously in patients with impaired liver function. Longer intervals between dose adjustments should be utilized to allow full assessment of response.**

Clinical Trials

A four-week, double-blind, placebo-controlled dose-response trial was conducted in 138 patients with type 2 diabetes using doses ranging from 0.25 to 4 mg taken with each of three meals. PRANDIN therapy resulted in dose-proportional glucose lowering over the full dose range. Plasma insulin levels increased after meals and reverted toward baseline before the next meal. Most of the fasting blood glucose-lowering effect was demonstrated within 1-2 weeks.

In a double-blind, placebo-controlled, 3-month dose titration study, PRANDIN or placebo doses for each patient were increased weekly from 0.25 mg through 0.5, 1, and 2 mg, to a maximum of 4 mg, until a fasting

plasma glucose (FPG) level <160 mg/dL was achieved or the maximum dose reached. The dose that achieved the targeted control or the maximum dose was continued to end of study. FPG and 2-hour post-prandial glucose (PPG) increased in patients receiving placebo and decreased in patients treated with repaglinide. Differences between the repaglinide- and placebo-treated groups were -61 mg/dL (FPG) and -104 mg/dL (PPG). The between-group change in HbA_{1c}, which reflects long-term glycemic control, was 1.7% units.

PRANDIN vs. Placebo Treatment: Mean FPG, PPG, and HbA_{1c} Changes from baseline after 3 months of treatment:

	FPG (mg/dL)		PPG (mg/dL)		HbA_{1c} (%)	
	PL	R	PL	R	PL	R
Baseline	215.3	220.2	245.2	261.7	8.1	8.5
Change from Baseline (at last visit)	30.3	-31.0*	56.5	-47.6*	1.1	-0.6*

FPG = fasting plasma glucose
PPG = post-prandial glucose
PL = placebo (N=33)
R = repaglinide (N=66)
*: $p < 0.05$ for between group difference

Another double-blind, placebo-controlled trial was carried out in 362 patients treated for 24 weeks. The efficacy of 1 and 4 mg preprandial doses was demonstrated by lowering of fasting blood glucose and by HbA_{1c} at the end of the study. HbA_{1c}, for the PRANDIN-treated groups (1 and 4 mg groups combined) at the end of the study was decreased compared to the

placebo-treated group in previously naïve patients and in patients previously treated with oral hypoglycemic agents by 2.1% units and 1.7% units, respectively. In this fixed-dose trial, patients who were naïve to oral hypoglycemic agent therapy and patients in relatively good glycemic control at baseline (HbA_{1c} below 8%) showed greater blood glucose-lowering including a higher frequency of hypoglycemia. Patients who were previously treated and who had baseline $HbA_{1c} \geq 8\%$ reported hypoglycemia at the same rate as patients randomized to placebo. There was no average gain in body weight when patients previously treated with oral hypoglycemic agents were switched to PRANDIN. The average weight gain in patients treated with PRANDIN and not previously treated with sulfonylurea drugs was 3.3%.

The dosing of PRANDIN relative to meal-related insulin release was studied in three trials including 58 patients. Glycemic control was maintained during a period in which the meal and dosing pattern was varied (2, 3 or 4 meals per day; before meals x 2, 3, or 4) compared with a period of 3 regular meals and 3 doses per day (before meals x 3). It was also shown that PRANDIN can be administered at the start of a meal, 15 minutes before, or 30 minutes before the meal with the same blood glucose-lowering effect.

PRANDIN was compared to other insulin secretagogues in 1-year controlled trials to demonstrate comparability of efficacy and safety. Hypoglycemia was reported in 16% of 1228 PRANDIN patients, 20% of 417 glyburide patients, and 19% of 81 glipizide patients. Of PRANDIN-treated patients with symptomatic hypoglycemia, none developed coma or required hospitalization.

PRANDIN was studied in combination with metformin in 83 patients not satisfactorily controlled on exercise, diet, and metformin alone. PRANDIN dosage was titrated for 4 to 8 weeks, followed by a 3-month maintenance period. Combination therapy with PRANDIN and metformin resulted in significantly greater improvement in glycemic control as compared to repaglinide or metformin monotherapy. HbA_{1c} was improved by 1% unit and FPG decreased by an additional 35 mg/dL. In this study where metformin dosage was kept constant, the combination therapy of PRANDIN and metformin showed dose-sparing effects with respect to PRANDIN. The greater efficacy response of the combination group was achieved at a lower daily repaglinide dosage than in the PRANDIN monotherapy group (see Table).

PRANDIN and Metformin Therapy: Mean Changes from Baseline in Glycemic Parameters and Weight After 4 to 5 Months of Treatment[1]

	PRANDIN	Combination	Metformin
N	28	27	27
Median Final Dose (mg/day)	12	6 (PRANDIN) 1500 (metformin)	1500
HbA_{1c} (% units)	-0.38	-1.41*	-0.33
FPG (mg/dL)	8.8	-39.2*	-4.5
Weight (kg)	3.0	2.4 #	-0.90

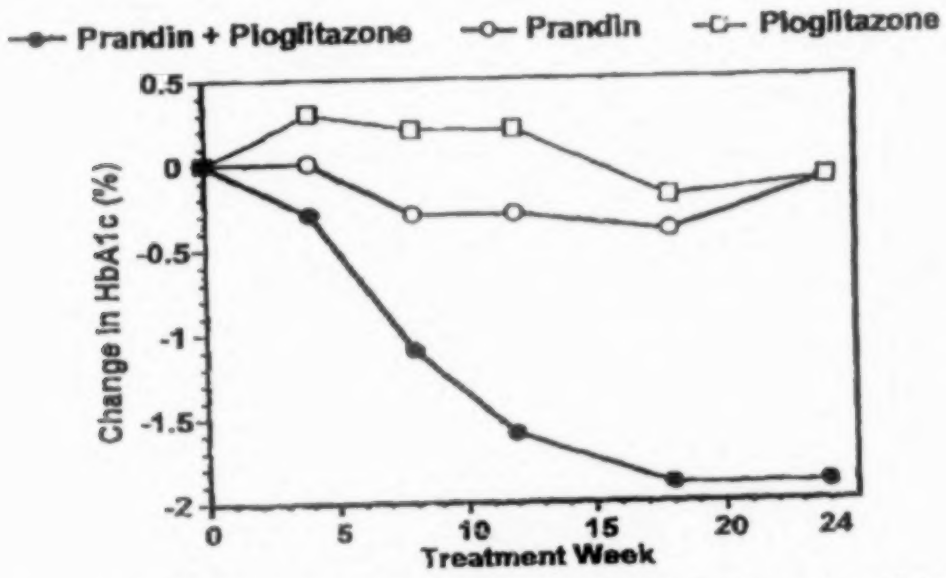
1: based on intent-to-treat analysis

*: $p < 0.05$, for pairwise comparisons with PRANDIN and metformin.

#: $p < 0.05$, for pairwise comparison with metformin.

A combination therapy regimen of PRANDIN and pioglitazone was compared to monotherapy with either agent alone in a 24-week trial that enrolled 246 patients previously treated with sulfonylurea or metformin monotherapy ($HbA_{1c} > 7.0\%$). Numbers of patients treated were: PRANDIN (N = 61), pioglitazone (N = 62), combination (N = 123). PRANDIN dosage was titrated during the first 12 weeks, followed by a 12-week maintenance period. Combination therapy resulted in significantly greater improvement in glycemic control as compared to monotherapy (figure below). The changes from baseline for completers in FPG (mg/dL) and HbA_{1c} (%), respectively were: -39.8 and -0.1 for PRANDIN, -35.3 and -0.1 for pioglitazone and -92.4 and -1.9 for the combination. In this study where pioglitazone dosage was kept constant, the combination therapy group showed dose-sparing effects with respect to PRANDIN (see figure legend). The greater efficacy response of the combination group was achieved at a lower daily repaglinide dosage than in the PRANDIN monotherapy group. Mean weight increases associated with combination, PRANDIN and pioglitazone therapy were 5.5 kg, 0.3 kg, and 2.0 kg respectively.

HbA_{1c} Values from PRANDIN / Pioglitazone Combination Study



HbA_{1c} values by study week for patients who completed study (combination, N = 101; PRANDIN, N = 35, pioglitazone, N = 26).
Subjects with FPG above 270 mg/dL were withdrawn from the study.
Pioglitazone dose: fixed at 30 mg/day; PRANDIN median final dose: 6 mg/day for combination and 10 mg/day for monotherapy.

A combination therapy regimen of PRANDIN and rosiglitazone was compared to monotherapy with either agent alone in a 24-week trial that enrolled 252 patients previously treated with sulfonylurea or metformin (HbA_{1c} > 7.0%). Combination therapy resulted in significantly greater improvement in glycemic control as compared to monotherapy (table below). The glycemic effects of the combination therapy were dose-sparing with respect to both total daily PRANDIN dosage and total daily rosiglitazone dosage (see table legend). A greater efficacy response of the combination therapy group was achieved with half the median daily

dose of PRANDIN and rosiglitazone, as compared to the respective monotherapy groups. Mean weight change associated with combination therapy was greater than that of PRANDIN monotherapy.

Mean Changes from Baseline in Glycemic Parameters and Weight in a 24-Week PRANDIN/ Rosiglitazone Combination Study[1]

	PRANDIN	Combination	Rosiglitazone
N	63	127	62
HbA_{1c} (%)			
Baseline	9.3	9.1	9.0
Change by 24 weeks	-0.17	-1.43*	-0.56
FPG (mg/dL)			
Baseline	269	257	252
Change by 24 weeks	-54	-94*	-67
Change in Weight (kg)	+1.3	+4.5 #	+3.3

1: based on intent-to-treat analysis

*: p-value ≤ 0.001 for comparison to either monotherapy

#: p-value < 0.001 for comparison to PRANDIN

Final median doses: rosiglitazone - 4 mg/day for combination and 8 mg/day for monotherapy;
PRANDIN - 6 mg/day for combination and 12 mg/day for monotherapy

INDICATIONS AND USAGE

PRANDIN is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with type 2 diabetes mellitus (NIDDM) whose hyperglycemia can-

not be controlled satisfactorily by diet and exercise alone.

PRANDIN is also indicated for combination therapy use (with metformin or thiazolidinediones) to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise plus monotherapy with any of the following agents: metformin, sulfonylureas, repaglinide, or thiazolidinediones. If glucose control has not been achieved after a suitable trial of combination therapy, consideration should be given to discontinuing these drugs and using insulin. Judgments should be based on regular clinical and laboratory evaluations.

In initiating treatment for patients with type 2 diabetes, diet and exercise should be emphasized as the primary form of treatment. Caloric restriction, weight loss, and exercise are essential in the obese diabetic patient. Proper dietary management and exercise alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. In addition to regular physical activity, cardiovascular risk factors should be identified and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral blood glucose-lowering agent or insulin should be considered. Use of PRANDIN must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone may be transient, thus requiring only short-term administration of PRANDIN.

During maintenance programs, PRANDIN should be discontinued if satisfactory lowering of blood glucose is

no longer achieved. Judgments should be based on regular clinical and laboratory evaluations.

In considering the use of PRANDIN or other antidiabetic therapies, it should be recognized that blood glucose control in type 2 diabetes has not been definitely established to be effective in preventing the long-tenn cardiovascular complications of diabetes. However, in patients with Type 1 diabetes, the Diabetes Control and Complications Trial (DCCT) demonstrated that improved glycemic control, as reflected by HbA_1c and fasting glucose levels, was associated with a reduction in the diabetic complications retinopathy, neuropathy, and nephropathy.

CONTRAINDICATIONS

PRANDIN is contraindicated in patients with:

1. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
2. Type1 diabetes.
3. Known hypersensitivity to the drug or its inactive ingredients.

PRECAUTIONS

General: PRANDIN is not indicated for use in combination with NPH-insulin (See **ADVERSE REACTIONS, Cardiovascular Events**)

Hypoglycemia: All oral blood glucose-lowering drugs including repaglinide are capable of producing hypoglycemia. Proper patient selection, dosage, and instructions to the patients are important to avoid hypoglycemic episodes. Hepatic insufficiency may cause elevated repaglinide blood levels and may diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemia. Elderly, debilitated, or malnourished patients, and those with adrenal, pituitary, he-

patic, or severe renal insufficiency may be particularly susceptible to the hypoglycemic action of glucose-lowering drugs.

Hypoglycemia may be difficult to recognize in the elderly and in people taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

The frequency of hypoglycemia is greater in patients with type 2 diabetes who have not been previously treated with oral blood glucose-lowering drugs (naïve) or whose HbA_{1c} is less than 8%. PRANDIN should be administered with meals to lessen the risk of hypoglycemia.

Loss of Control of Blood Glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of glycemic control may occur. At such times, it may be necessary to discontinue PRANDIN and administer insulin. The effectiveness of any hypoglycemic drug in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when the drug is first given. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

Information for Patients

Patients should be informed of the potential risks and advantages of PRANDIN and of alternative modes of

therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose and HbA_{1c}. The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development and concomitant administration of other glucose-lowering drugs should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Patients should be instructed to take PRANDIN before meals (2, 3, or 4 times a day preprandially). Doses are usually taken within 15 minutes of the meal but time may vary from immediately preceding the meal to as long as 30 minutes before the meal. **Patients who skip a meal (or add an extra meal) should be instructed to skip (or add) a dose for that meal.**

Laboratory Tests

Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels with a goal of decreasing these levels towards the normal range. During dose adjustment, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Glycosylated hemoglobin may be especially useful for evaluating long-term glycemic control. Postprandial glucose level testing may be clinically helpful in patients whose pre-meal blood glucose levels are satisfactory but whose overall glycemic control (HbA_{1c}) is inadequate.

Drug-Drug Interactions

In vitro data indicate that repaglinide metabolism may be inhibited by antifungal agents like ketoconazole and miconazole, and antibacterial agents

like erythromycin (cytochrome P-450 enzyme system 3A4 inhibitors). Drugs that induce the cytochrome P450 enzyme system 3A4 may increase repaglinide metabolism; such drugs include rifampin, barbiturates, and carbamezapine. See **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions.**

In vivo data from a study that evaluated the coadministration of a cytochrome P450 enzyme inhibitor, clarithromycin, with PRANDIN resulted in a clinically significant increase in repaglinide plasma levels. This increase in repaglinide plasma levels may necessitate a PRANDIN dose adjustment. See **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions.**

In vivo data from a study that evaluated the coadministration of gemfibrozil with PRANDIN in healthy subjects resulted in a significant increase in repaglinide blood levels. **Patients taking PRANDIN should not start taking gemfibrozil; patients taking gemfibrozil should not start taking PRANDIN. Concomitant use may result in enhanced and prolonged blood glucose-lowering effects of repaglinide. Caution should be used in patients already on PRANDIN and gemfibrozil - blood glucose levels should be monitored and PRANDIN dose adjustment may be needed. Rare postmarketing events of serious hypoglycemia have been reported in patients taking PRANDIN and gemfibrozil together. Gemfibrozil and itraconazole had a synergistic metabolic inhibitory effect on PRANDIN. Therefore, patients taking PRANDIN and gemfibrozil should not take itraconazole.** See **CLINICAL PHARMACOLOGY** section, **Drug-Drug Interactions.**

The hypoglycemic action of oral blood glucose-lowering agents may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving oral blood glucose-lowering agents, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving oral blood glucose-lowering agents, the patient should be observed closely for loss of glycemic control.

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When these drugs are administered to a patient receiving oral blood glucose-lowering agents, the patient should be observed for loss of glycemic control. When these drugs are withdrawn from a patient receiving oral blood glucose-lowering agents, the patient should be observed closely for hypoglycemia.

Carcinogenesis, Mutagenesis, and Impairment Of Fertility

Long-term carcinogenicity studies were performed for 104 weeks at doses up to and including 120 mg/kg body weight/day (rats) and 500 mg/kg body weight/day (mice) or approximately 60 and 125 times clinical exposure, respectively, on a mg/m^2 basis. No evidence of carcinogenicity was found in mice or female rats. In male rats, there was an increased incidence of benign adenomas of the thyroid and liver. The relevance of

these findings to humans is unclear. The no-effect doses for these observations in male rats were 30 mg/kg body weight/day for thyroid tumors and 60 mg/kg body weight/day for liver tumors, which are over 15 and 30 times, respectively, clinical exposure on a mg/m^2 basis.

Repaglinide was non-genotoxic in a battery of *in vivo* and *in vitro* studies: Bacterial mutagenesis (Ames test), *in vitro* forward cell mutation assay in V79 cells (HGPRT), *in vitro* chromosomal aberration assay in human lymphocytes, unscheduled and replicating DNA synthesis in rat liver, and *in vivo* mouse and rat micronucleus tests.

Fertility of male and female rats was unaffected by repaglinide administration at doses up to 80 mg/kg body weight/day (females) and 300 mg/kg body weight/day (males); over 40 times clinical exposure on a mg/m^2 basis.

Pregnancy

Pregnancy category C

Teratogenic Effects: Safety in pregnant women has not been established. Repaglinide was not teratogenic in rats or rabbits at doses 40 times (rats) and approximately 0.8 times (rabbit) clinical exposure (on a mg/m^2 basis) throughout pregnancy. Because animal reproduction studies are not always predictive of human response, PRANDIN should be used during pregnancy only if it is clearly needed.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to

normal as possible.

Nonteratogenic Effects: Offspring of rat dams exposed to repaglinide at 15 times clinical exposure on a mg/m^2 basis during days 17 to 22 of gestation and during lactation developed nonteratogenic skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. This effect was not seen at doses up to 2.5 times clinical exposure (on a mg/m^2 basis) on days 1 to 22 of pregnancy or at higher doses given during days 1 to 16 of pregnancy. Relevant human exposure has not occurred to date and therefore the safety of PRANDIN administration throughout pregnancy or lactation cannot be established.

Nursing Mothers

In rat reproduction studies, measurable levels of repaglinide were detected in the breast milk of the dams and lowered blood glucose levels were observed in the pups. Cross fostering studies indicated that skeletal changes (see **Nonteratogenic Effects**) could be induced in control pups nursed by treated dams, although this occurred to a lesser degree than those pups treated *in utero*. Although it is not known whether repaglinide is excreted in human milk some oral agents are known to be excreted by this route. Because the potential for hypoglycemia in nursing infants may exist, and because of the effects on nursing animals, a decision should be made as to whether PRANDIN should be discontinued in nursing mothers, or if mothers should discontinue nursing. If PRANDIN is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

No studies have been performed in pediatric patients.

Geriatric Use

In repaglinide clinical studies of 24 weeks or greater duration, 415 patients were over 65 years of age. In one-year, active-controlled trials, no differences were seen in effectiveness or adverse events between these subjects and those less than 65 other than the expected age-related increase in cardiovascular events observed for PRANDIN and comparator drugs. There was no increase in frequency or severity of hypoglycemia in older subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals to PRANDIN therapy cannot be ruled out.

ADVERSE REACTIONS

Hypoglycemia: See **PRECAUTIONS and OVERDOSAGE** sections.

PRANDIN has been administered to 2931 individuals during clinical trials. Approximately 1500 of these individuals with type 2 diabetes have been treated for at least 3 months, 1000 for at least 6 months, and 800 for at least 1 year. The majority of these individuals (1228) received PRANDIN in one of five 1-year, active-controlled trials. The comparator drugs in these 1-year trials were oral sulfonylurea drugs (SU) including glyburide and glipizide. Over one year, 13% of PRANDIN patients were discontinued due to adverse events, as were 14% of SU patients. The most common adverse events leading to withdrawal were hyperglycemia, hypoglycemia, and related symptoms (see **PRECAUTIONS**). Mild or moderate hypoglycemia occurred in 16% of PRANDIN patients, 20% of glyburide patients, and 19% of glipizide patients.

The table below lists common adverse events for

PRANDIN patients compared to both placebo (in trials 12 to 24 weeks duration) and to glyburide and glipizide in one year trials. The adverse event profile of PRANDIN was generally comparable to that for sulfonylurea drugs (SU).

Commonly Reported Adverse Events (% of Patients)*

EVENT	PRANDIN N = 352	PLACEBO N =108	PRANDIN N = 1228	SU N = 498
	Placebo controlled studies		Active controlled studies	
Metabolic				
Hypoglycemia	31**	7	16	20
Respiratory				
URI	16	8	10	10
Sinusitis	6	2	3	4
Rhinitis	3	3	7	8
Bronchitis	2	1	6	7
Gastrointestinal				
Nausea	5	5	3	2
Diarrhea	5	2	4	6
Constipation	3	2	2	3
Vomiting	3	3	2	1
Dyspepsia	2	2	4	2
Musculoskeletal				
Arthralgia	6	3	3	4
Back Pain	5	4	6	7
Other				
Headache	11	10	9	8

Paresthesia	3	3	2	1
Chest pain	3	1	2	1
Urinary tract infection	2	1	3	3
Tooth disorder	2	0	<1	<1
Allergy	2	0	1	<1

*: Events ≥2% for the PRANDIN group in the placebo-controlled studies and ≥ events in the placebo group

: See trial description in **CLINICAL PHARMACOLOGY, Clinical Trials

Cardiovascular Events

In one-year trials comparing Prandin to sulfonylurea drugs, the incidence of angina was comparable (1.8%) for both treatments, with an incidence of chest pain of 1.8% for PRANDIN and 1.0% for sulfonylureas. The incidence of other selected cardiovascular events (hypertension, abnormal EKG, myocardial infarction, arrhythmias, and palpitations) was ≤ 1% and not different between PRANDIN and the comparator drugs.

The incidence of total serious cardiovascular adverse events, including ischemia, was higher for repaglinide (4%) than for sulfonylurea drugs (3%) in controlled comparator clinical trials. In 1-year controlled trials, PRANDIN treatment was not associated with excess mortality when compared to the rates observed with other oral hypoglycemic agent therapies.

Summary of Serious Cardiovascular Events (% of total patients with events) in Trials Comparing Prandin to Sulfonylureas

	PRANDIN	SU*
Total Exposed	1228	498

Serious CV Events	4%	3%
Cardiac Ischemic Events	2%	2%
Deaths due to CV Events	0.5%	0.4%

*: glyburide and glipizide

Seven controlled clinical trials included PRANDIN combination therapy with NPH-insulin (n=431), insulin formulations alone (n=388) or other combinations (sulfonylurea plus NPH-insulin or PRANDIN plus metformin) (n=120). There were six serious adverse events of myocardial ischemia in patients treated with Prandin plus NPH-insulin from two studies, and one event in patients using insulin formulations alone from another study.

Infrequent Adverse Events (<1% of Patients)

Less common adverse clinical or laboratory events observed in clinical trials included elevated liver enzymes, thrombocytopenia, leukopenia, and anaphylactoid reactions (one patient).

Combination Therapy with Thiazolidinediones

During 24-week treatment clinical trials of PRANDIN-rosiglitazone or PRANDIN-pioglitazone combination therapy (a total of 250 patients in combination therapy), hypoglycemia (blood glucose < 50 mg/dL) occurred in 7% of combination therapy patients in comparison to 7% for PRANDIN monotherapy, and 2% for thiazolidinedione monotherapy.

Peripheral edema was reported in 12 out of 250 PRANDIN-thiazolidinedione combination therapy patients and 3 out of 124 thiazolidinedione monotherapy patients, with no cases reported in these trials for

PRANDIN monotherapy. When corrected for dropout rates of the treatment groups, the percentage of patients having events of peripheral edema per 24 weeks of treatment were 5% for PRANDIN-thiazolidinedione combination therapy, and 4% for thiazolidinedione monotherapy. There were reports in 2 of 250 patients (0.8%) treated with PRANDIN-thiazolidinedione therapy of episodes of edema with congestive heart failure. Both patients had a prior history of coronary artery disease and recovered after treatment with diuretic agents. No comparable cases in the monotherapy treatment groups were reported.

Mean change in weight from baseline was +4.9 kg for PRANDIN-thiazolidinedione therapy. There were no patients on PRANDIN-thiazolidinedione combination therapy who had elevations of liver transaminases (defined as 3 times the upper limit of normal levels). Although no causal relationship has been established, postmarketing experience includes reports of the following rare adverse events: alopecia, hemolytic anemia, pancreatitis, Stevens-Johnson Syndrome, and severe hepatic dysfunction.

OVERDOSAGE

In a clinical trial, patients received increasing doses of PRANDIN up to 80 mg a day for 14 days. There were few adverse effects other than those associated with the intended effect of lowering blood glucose. Hypoglycemia did not occur when meals were given with these high doses. Hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring may continue until the physician is assured that the patient is out of danger. Patients should be closely mo-

nitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery. There is no evidence that repaglinide is dialyzable using hemodialysis.

Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of type 2 diabetes with PRANDIN.

The patient's blood glucose should be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e., loss of an adequate blood glucose-lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels are of value in monitoring the patient's longer term response to therapy.

Short-term administration of PRANDIN may be sufficient during periods of transient loss of control in patients usually well controlled on diet.

PRANDIN doses are usually taken within 15 minutes of the meal but time may vary from immediately preceding the meal to as long as 30 minutes before the meal.

Starting Dose

For patients not previously treated or whose HbA_{1c} is < 8%, the starting dose should be 0.5 mg with each meal. For patients previously treated with blood glucose-lowering drugs and whose HbA_{1c} is ≥ 8%, the initial dose is 1 or 2 mg with each meal preprandially (see previous paragraph).

Dose Adjustment

Dosing adjustments should be determined by blood glucose response, usually fasting blood glucose. Postprandial glucose levels testing may be clinically helpful in patients whose pre-meal blood glucose levels are satisfactory but whose overall glycemic control (HbA_{1c}) is inadequate. The preprandial dose should be doubled up to 4 mg with each meal until satisfactory blood glucose response is achieved. At least one week should elapse to assess response after each dose adjustment.

The recommended dose range is 0.5 mg to 4 mg taken with meals. PRANDIN may be dosed preprandially 2, 3, or 4 times a day in response to changes in the patient's meal pattern. The maximum recommended daily dose is 16 mg.

Patient Management

Long-term efficacy should be monitored by measurement of HbA_{1c} levels approximately every 3 months. Failure to follow an appropriate dosage regimen may precipitate hypoglycemia or hyperglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy including hypoglycemia. When hypoglycemia occurs in patients taking a combination of PRANDIN and a thiazolidinedione or PRANDIN and metformin, the dose of PRANDIN should be reduced.

Patients Receiving Other Oral Hypoglycemic Agents

When PRANDIN is used to replace therapy with other oral hypoglycemic agents, PRANDIN may be started on the day after the final dose is given. Patients should then be observed carefully for hypoglycemia due to potential overlapping of drug effects. When transferred from longer half-life sulfonylurea agents (e.g., chlorpropamide) to repaglinide, close monitoring may be indicated for up to one week or longer.

Combination Therapy

If PRANDIN monotherapy does not result in adequate glycemic control, metformin or a thiazolidinedione may be added. If metformin or thiazolidinedione monotherapy does not provide adequate control, PRANDIN may be added. The starting dose and dose adjustments for PRANDIN combination therapy is the same as for PRANDIN monotherapy. The dose of each drug should be carefully adjusted to determine the minimal dose required to achieve the desired pharmacologic effect. Failure to do so could result in an increase in the incidence of hypoglycemic episodes. Appropriate monitoring of FPG and HbA_{1c} measurements should be used to ensure that the patient is not subjected to excessive drug exposure or increased probability of secondary drug failure.

HOW SUPPLIED

PRANDIN (repaglinide) tablets are supplied as unscored, biconvex tablets available in 0.5 mg (white), 1 mg (yellow) and 2 mg (peach) strengths. Tablets are embossed with the Novo Nordisk (Apis) bull symbol and colored to indicate strength.

0.5 mg tablets (white)	Bottles of 100	NDC 00169-0081-81
	Bottles of 500	NDC 00169-0081-82
	Bottles of 1000	NDC 00169-0081-83
1 mg tablets (yellow)	Bottles of 100	NDC 00169-0082-81
	Bottles of 500	NDC 00169-0082-82
	Bottles of 1000	NDC 00169-0082-83
2 mg tablets (peach)	Bottles of 100	NDC 00169-0084-81
	Bottles of 500	NDC 00169-0084-82
	Bottles of 1000	NDC 00169-0084-83

Do not store above 25° C (77° F).

Protect from moisture. Keep bottles tightly closed. Dispense in tight containers with safety closures.

Licensed Under US Patent Nos. RE 37,035, 5,312,924 and 6,143,769

PRANDIN® is a registered trademark of Novo Nordisk A/S.

Manufactured in Germany for
Novo Nordisk Inc.
Princeton, NJ 08540
1-800-727-6500
www.novonordisk-us.com

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December, 2004

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

Civil Action No.: 2:05 CV 40188
Hon. Avern Cohn

EXHIBIT F TO THE DECLARATION OF DAVID L. ROSEN

FILED UNDER SEAL PURSUANT TO PROTECTIVE ORDER (DOCKET NO. 40)

* * * *

[Exhibit F Reproduced at JA 163 - 165]

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

Civil Action No.: 2:05 CV 40188
Hon. Avern Cohn

EXHIBIT G TO THE DECLARATION OF DAVID L. ROSEN

* * * *

[Exhibit G Reproduced at JA 15 - 48]

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

Civil Action No.: 2:05 CV 40188
Hon. Avern Cohn

EXHIBIT H TO THE DECLARATION OF DAVID L. ROSEN

FILED UNDER SEAL PURSUANT TO PROTECTIVE ORDER (DOCKET NO. 40)

Novo Nordisk

May 6, 2009

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville MD 20705-1266

Re: TIME SENSITIVE PATENT INFORMATION NDA 20-741, Prandin® (repaglinide)

To the Orange Book Staff:

In accordance with Section 314.53(c) and (d) of FDA regulations, please find an original and two copies of

Form FDA 3542, containing an AMENDMENT to the patent information for the above-referenced NDA. The information being submitted is to amend the use code relating to U.S. Patent No. 6,677,358 to correspond with the change in labeling required by FDA in November 28, 2007 (and to correct an unrelated inadvertent error in the original Form 3542.) This amendment is not applicable to NDA 22-386, PrandiMet® (metformin hydrochloride/ repaglinide), which will retain its present use code relating to U.S. Patent No. 6,677,358.

Applicant believes the use code should be changed. Therefore, please remove use code U-546 from the Orange Book for the listed drug (Prandin) and substitute with the use code contained in this form.

Sincerely,

/s/ James C. Shehan/RRWO
James C. Shehan
Vice President and General Counsel

RECEIVED
MAY 07 2009
[Illegible]

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 2.

PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation or Composition) and/or Method of Use

NDA NUMBER
20-741

NAME OF APPLICANT/NDA HOLDER
Novo Nordisk Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act:

TRADE NAME
Prandin

ACTIVE INGREDIENT(S)	STRENGTH(S)
repaglinide	0.5 mg 1.0 mg 2.0 mg

DOSAGE FORM	APPROVAL DATE OF NDA OR SUPPLEMENT
Tablet, oral	December 22, 1997

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) within thirty (30) days after approval of an NDA or supplement or within thirty (30) days of issuance of a patent as required by 21 CFR 314.53(c)(2)(ii) at the address provided in 21 CFR 314.53(d)(4). To expedite review of this patent declaration form, you may submit an additional copy of this declaration form to the Center for Drug Evaluation and Research "Orange Book" staff.

For hand-written or typewriter versions of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
US 6677358	January 13, 2004	June 12, 2018

d. Name of Patent Owner	Address (*of Patent Owner*)	
Novo Nordisk A/S	Novo Alle	
	City/State DK-2800, Bagsvaerd DENMARK	
	ZIP Code	FAX Number (*if available*) (454) 443-7799
	Telephone Number (454) 442-2247	E-Mail Address (*if available*)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (If patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (*of agent or representative named in f. e.*)	
☞ Chief Patent Counsel	100 College Road West	
	City/State Princeton, NJ	
	ZIP Code 08540	FAX Number (*if available*) (609) 987-5440
	Telephone Number (609) 987-5800	E-Mail Address (*if available*)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☑ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☑ No

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For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement?	☐ Yes	☑ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA?	☐ Yes	☑ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.)	☐ Yes	☑ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug substance if:

- the answers to 2.1 and 2.2 are "No," or,
- the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,
- the answer to 2.3 is "Yes" and there is no response to 2.4, or,
- the answer to 2.5 or 2.6 is "Yes."
- the answer to 2.7 is "No."

3. Drug Product (Composition, Formulation)

3.1 Does the patent claim the approved drug product as defined in 21 CFR 314.3?	☑ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug product if:

- the answer to question 3.1 is "No," or,
- the answer to question 3.2 is "Yes," or,
- the answer to question 3.3 is "No."

4. Method of Use

Sponsors must submit the information in section 4 for each approved method of using the approved drug product claimed by the patent. For each approved method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more approved methods of using the approved drug product?		☑ Yes	☐ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in 4.2 claim an approved method of use of the approved drug product?	☑ Yes	☐ No
Claim 4			
4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the approved labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* INDICATIONS AND USAGE: As adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus; CLINICAL PHARMACOLOGY (Combination Trials) and DOSAGE & ADMINISTRATION sections of the approved label.		

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NOVO-6901137

4.2b If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description.	Use: *(Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)* A method for improving glycemic control in adults with type 2 diabetes mellitus.

FDA will not list the patent in the Orange Book as claiming the method of use if:

- the answer to question 4.1 or 4.2 is "No," or
- If the answer to 4.2 is "Yes" and the information requested in 4.2a and 4.2b is not provided in full.

5. No Relevant Patents

For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration and Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official)* *(Provide information below)*	Date Signed
James C Shehan /RRW	05/06/2009

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/ holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name James C. Shehan, General Counsel	
Address 100 College Road West	City/State Princeton, NJ
ZIP Code 08940	Telephone Number (609) 987-5800
FAX Number *(If available)*	E-Mail Address *(If available)*

The public reporting burden for this collection of information has been estimated to average 5 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542

PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use. Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the approved NDA or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be listed. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be listed as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the approved NDA or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims one or more methods of use of the drug product that is the subject of the approved NDA or supplement.

4.2) For each approved use of the drug claimed by the patent, identify by number the claim(s) in the patent that claim the approved use of the drug. An applicant may list together multiple patent claim numbers and information for each approved method of use, if applicable. However, each approved method of use must be separately listed within this section of the form.

4.2a) Specify the part of the approved drug labeling that is claimed by the patent.

4.2b) The answer to this question will be what FDA uses to create a "use-code" for Orange Book publication. The use code designates a method of use patent that claims the approved indication or use of a drug product. Each approved use claimed by the patent should be separately identified in this section and contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method of use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval. Use a maximum of 240 characters for each "use code."

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

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NOVO-6901139

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

Civil Action No.: 2:05 CV 40188
Hon. Avern Cohn

EXHIBIT I TO THE DECLARATION OF DAVID L. ROSEN

GLUCOVANCE®

(Glyburide and Metformin HCl) Tablets

1.25 mg/250 mg

2.5 mg/500 mg

5 mg/500 mg

DESCRIPTION

GLUCOVANCE® (Glyburide and Metformin HCl) Tablets contain 2 oral antihyperglycemic drugs used in the management of type 2 diabetes, glyburide and metformin hydrochloride.

Glyburide is an oral antihyperglycemic drug of the sulfonylurea class. The chemical name for glyburide is 1-[[*p*-[2-(5-chloro-*o*-anisamido)ethyl]phenyl]sulfonyl]-

3-cyclo-hexylurea. Glyburide is a white to off-white crystalline compound with a molecular formula of $C_{23}H_{28}ClN_3O_5S$ and a molecular weight of 494.01. The glyburide used in GLUCOVANCE has a particle size distribution of 25% undersize value not more than 6 µm, 50% undersize value not more than 7 to 10 µm, and 75% undersize value not more than 21 µm. The structural formula is represented below.

Metformin hydrochloride is an oral antihyperglycemic drug used in the management of type 2 diabetes. Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide monohydrochloride) is not chemically or pharmacologically related to sulfonylureas, thiazolidinediones, or α-glucosidase inhibitors. It is a white to off-white crystalline compound with a molecular formula of $C_4H_{12}ClN_5$ (monohydrochloride) and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is as shown:

GLUCOVANCE is available for oral administration in tablets containing 1.25 mg glyburide with 250 mg metformin hydrochloride, 2.5 mg glyburide with 500 mg metformin hydrochloride, and 5 mg glyburide with 500 mg metformin hydrochloride. In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, povidone, croscarmellose sodium, and magnesium stearate. The tablets are film coated, which provides color differentiation.

CLINICAL PHARMACOLOGY

Mechanism of Action

GLUCOVANCE combines glyburide and metformin hydrochloride, 2 antihyperglycemic agents with complementary mechanisms of action, to improve glycemic control in patients with type 2 diabetes.

Glyburide appears to lower blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which glyburide lowers blood glucose during long-term administration has not been clearly established. With chronic administration in patients with type 2 diabetes, the blood glucose-lowering effect persists despite a gradual decline in the insulin secretory response to the drug. Extrapancreatic effects may be involved in the mechanism of action of oral sulfonylurea hypog-

lycemic drugs.

Metformin hydrochloride is an antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin hydrochloride decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

* * * *

INDICATIONS AND USAGE

GLUCOVANCE (Glyburide and Metformin HCl) Tablets is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

* * * *

DOSAGE AND ADMINISTRATION

General Considerations

Dosage of GLUCOVANCE must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended daily dose of 20 mg glyburide/2000 mg metformin. GLUCOVANCE should be given with meals and should be initiated at a low dose, with gradual dose escalation as described below, in order to avoid hypoglycemia (largely due to glyburide), reduce GI side effects (largely due to metformin), and permit determination of the minimum effective dose for adequate control of blood glucose for the individual patient.

With initial treatment and during dose titration, appropriate blood glucose monitoring should be used to

determine the therapeutic response to GLUCOVANCE and to identify the minimum effective dose for the patient. Thereafter, HbA_{1c}, should be measured at intervals of approximately 3 months to assess the effectiveness of therapy. The therapeutic goal in all patients with type 2 diabetes is to decrease FPG, PPG, and HbA_{1c} to normal or as near normal as possible. Ideally, the response to therapy should be evaluated using HbA_{1c} (glycosylated hemoglobin), which is a better indicator of long-term glycemic control than FPG alone.

No studies have been performed specifically examining the safety and efficacy of switching to GLUCOVANCE therapy in patients taking concomitant glyburide (or other sulfonylurea) plus metformin. Changes in glycemic control may occur in such patients, with either hyperglycemia or hypoglycemia possible. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring.

GLUCOVANCE in Patients with Inadequate Glycemic Control on Diet and Exercise

Recommended starting dose: 1.25 mg/250 mg once or twice daily with meals.

For patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone, the recommended starting dose of GLUCOVANCE is 1.25 mg/250 mg once a day with a meal. As initial therapy in patients with baseline HbA_{1c} >9% or an FPG >200 mg/dL, a starting dose of GLUCOVANCE 1.25 mg/250 mg twice daily with the morning and evening meals may be used. Dosage increases should be made in increments of 1.25 mg/250 mg per day every 2 weeks up to the minimum effective dose necessary to achieve adequate control of

blood glucose. In clinical trials of GLUCOVANCE as initial therapy, there was no experience with total daily doses >10 mg/2000 mg per day. **GLUCOVANCE 5 mg/500 mg should not be used as initial therapy due to an increased risk of hypoglycemia.**

GLUCOVANCE Use in Patients with Inadequate Glycemic Control on a Sulfonylurea and/or Metformin

Recommended starting dose: 2.5 mg/500 mg or 5 mg/500 mg twice daily with meals.

For patients not adequately controlled on either glyburide (or another sulfonylurea) or metformin alone, the recommended starting dose of GLUCOVANCE is 2.5 mg/500 mg or 5 mg/500 mg twice daily with the morning and evening meals. In order to avoid hypoglycemia, the starting dose of GLUCOVANCE should not exceed the daily doses of glyburide or metformin already being taken. The daily dose should be titrated in increments of no more than 5 mg/500 mg up to the minimum effective dose to achieve adequate control of blood glucose or to a maximum dose of 20 mg/2000 mg per day.

For patients previously treated with combination therapy of glyburide (or another sulfonylurea) plus metformin, if switched to GLUCOVANCE, the starting dose should not exceed the daily dose of glyburide (or equivalent dose of another sulfonylurea) and metformin already being taken. Patients should be monitored closely for signs and symptoms of hypoglycemia following such a switch and the dose of GLUCOVANCE should be titrated as described above to achieve adequate control of blood glucose.

Addition of Thiazolidinediones to GLUCOVANCE Therapy

For patients not adequately controlled on GLUCOVANCE, a thiazolidinedione can be added to GLUCOVANCE therapy. When a thiazolidinedione is added to GLUCOVANCE therapy, the current dose of GLUCOVANCE can be continued and the thiazolidinedione initiated at its recommended starting dose. For patients needing additional glycemic control, the dose of the thiazolidinedione can be increased based on its recommended titration schedule. The increased glycemic control attainable with GLUCOVANCE plus a thiazolidinedione may increase the potential for hypoglycemia at any time of day. In patients who develop hypoglycemia when receiving GLUCOVANCE and a thiazolidinedione, consideration should be given to reducing the dose of the glyburide component of GLUCOVANCE. As clinically warranted, adjustment of the dosages of the other components of the antidiabetic regimen should also be considered.

Specific Patient Populations

GLUCOVANCE is not recommended for use during pregnancy. The initial and maintenance dosing of GLUCOVANCE should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment requires a careful assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of GLUCOVANCE to avoid the risk of hypoglycemia. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly. (See **WARNINGS**.)

* * * *

Distributed by:

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

1158884A5

Rev July 2009

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

Civil Action No.: 2:05 CV 40188
Hon. Avern Cohn

EXHIBIT J TO THE DECLARATION OF DAVID L. ROSEN

NOVARTIS

Starlix®

(nateglinide) tablets

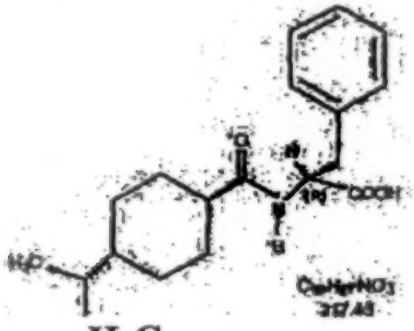
Rx only

Prescribing Information

DESCRIPTION

Starlix® (nateglinide) is an oral antidiabetic agent used in the management of Type 2 diabetes mellitus [also known as non-insulin dependent diabetes mellitus (NIDDM) or adult-onset diabetes]. Starlix, (-)-N-[(trans-4-isopropylcyclohexane)carbo-nyl]-D-phenylalanine, is structurally unrelated to the oral sulfonylurea insulin secretagogues.

The structural formula is as shown



H_3C

Nateglinide is a white powder with a molecular weight of 317.43. It is freely soluble in methanol, ethanol, and chloroform, soluble in ether, sparingly soluble in acetonitrile and octanol, and practically insoluble in water. Starlix biconvex tablets contain 60 mg, or 120 mg, of nateglinide for oral administration.

Inactive Ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, iron oxides (red or yellow), lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Nateglinide is an amino-acid derivative that lowers blood glucose levels by stimulating insulin secretion from the pancreas. This action is dependent upon functioning beta-cells in the pancreatic islets. Nateglinide interacts with the ATP-sensitive potassium ($K+_{ATP}$) channel on pancreatic beta-cells. The subsequent depolarization of the beta cell opens the calcium channel, producing calcium influx and insulin secretion. The extent of insulin release is glucose dependent and diminishes at low glucose levels. Nateglinide is highly tissue selective

with low affinity for heart and skeletal muscle.

* * * *

INDICATIONS AND USAGE

Starlix® (nateglinide) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

* * * *

DOSAGE AND ADMINISTRATION

Starlix® (nateglinide) should be taken 1 to 30 minutes prior to meals.

Monotherapy and Combination with Metformin or a Thiazolidinedione

The recommended starting and maintenance dose of Starlix, alone or in combination with metformin or a thiazolidinedione, is 120 mg three times daily before meals.

The 60-mg dose of Starlix, either alone or in combination with metformin or a thiazolidinedione, may be used in patients who are near goal HbA_{1C} when treatment is initiated.

Dosage in Geriatric Patients

No special dose adjustments are usually necessary. However, greater sensitivity of some individuals to Starlix therapy cannot be ruled out.

Dosage in Renal and Hepatic Impairment

No dosage adjustment is necessary in patients with mild-to-severe renal insufficiency or in patients with mild hepatic insufficiency. Dosing of patients with moderate-to-severe hepatic dysfunction has not been studied. Therefore, Starlix should be used with caution

in patients with moderate-to-severe liver disease (see PRECAUTIONS, Hepatic Impairment).

* * * *

REV: July 2008

NOVARTIS
Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
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UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

Civil Action No.: 2:05 CV 40188
Hon. Avern Cohn

EXHIBIT K TO THE DECLARATION OF DAVID L. ROSEN

Patent Use Codes

This page defines the patent use codes.

Code Definition

U PATENT USE CODE (SEE INDIVIDUAL REFERENCES)

U-1 PREVENTION OF PREGNANCY

U-2 TREATMENT OR PROPHYLAXIS OF ANGINA PECTORIS AND ARRHYTHMIA

U-3 TREATMENT OF HYPERTENSION

U-4 PROVIDING PREVENTION AND TREATMENT OF EMESIS AND NAUSEA IN MAMMALS

U-5 METHOD OF PRODUCING BRONCHODILATION

U-6 METHOD OF PRODUCING SYMPATHOMIMETIC EFFECTS

U-7 INCREASING CARDIAC CONTRACTILITY

U-8 ACUTE MYOCARDIAL INFARCTION

U-9 CONTROL OF EMESIS ASSOCIATED WITH ANY CANCER CHEMOTHERAPY AGENT

U-10 DIAGNOSTIC METHOD FOR DISTINGUISHING BETWEEN HYPOTHALMIC MALFUNCTIONS OR LESIONS IN HUMANS

U-11 TREATMENT OR PROPHYLAXIS OF CARDIAC DISORDERS

U-12 METHOD OF TREATING [A] HUMAN SUFFERING FROM DEPRESSION

U-13 A METHOD FOR TREATING ANXIETY IN A HUMAN SUBJECT IN NEED OF SUCH TREATMENT

U-14 ADJUNCTIVE THERAPY FOR THE PREVENTION AND TREATMENT OF HYPERAMMONEMIA IN THE CHRONIC MANAGEMENT OF PATIENTS WITH UREA CYCLE ENZYMOPATHIES

U-15 METHOD OF LOWERING INTRAOCULAR PRESSURE

U-16 USE IN LUNG SCANNING PROCEDURES

U-17 TREATMENT OF VENTRICULAR AND SUPRAVENTRICULAR ARRHYTHMIAS

U-18 METHOD FOR INHIBITING GASTRIC SECRETION IN MAMMALS

U-19 TREATMENT OF INFLAMMATION

U-20 A PROCESS FOR TREATING A PATIENT SUFFERING FROM PARKINSON'S SYNDROME AND IN NEED OF TREATMENT

U-21 TREATMENT OF HUMANS SUFFERING UNDESIRED UROTOXIC SIDE EFFECTS CAUSED BY CYTOSTATICALLY ACTIVE ALKYLATING AGENTS

U-22 METHOD OF COMBATTING PATHOLOGICALLY REDUCED CEREBRAL FUNCTIONS AND PERFORMANCE WEAKNESSES, CEREBRAL INSUFFICIENCY AND DISORDERS IN CEREBRAL CIRCULATION AND METABOLISM IN WARM-BLOODED ANIMALS

U-23 METHOD FOR TREATING PROSTATIC CARCINOMA COMPRISING ADMINISTERING FLUTAMIDE

U-24 METHOD FOR TREATING PROSTATE ADENOCARCINOMA COMPRISING ADMINISTERING AN ANTIANDROGEN INCLUDING FLUTAMIDE AND AN LHRH AGONIST

U-25 REDUCING CHOLESTEROL IN CHOLELITHIASIS PATIENTS

U-26 REDUCING CHOLESTEROL GALLSTONES AND/OR FRAGMENTS THEREOF

U-27 DISSOLVING CHOLESTEROL GALLSTONES AND/OR FRAGMENTS THEREOF

U-28 CEREBRAL, CORONARY, PERIPHERAL, VISCERAL AND RENAL ARTERIOGRAPHY, AORTOGRAPHY AND LEFT VENTRICULOGRAPHY

U-29 CT IMAGING OF THE HEAD AND BODY, AND INTRAVENOUS EXCRETORY UROGRAPHY

U-30 CEREBRAL ANGIOGRAPHY, AND VENOGRAPHY

U-31 INTRA-ARTERIAL DIGITAL SUBTRACTION ANGIOGRAPHY

U-32 PALLIATIVE TREATMENT OF PATIENTS WITH OVARIAN CARCINOMA RECURRENT AFTER PRIOR CHEMOTHERAPY, INCLUDING PATIENTS WHO HAVE BEEN PREVIOUSLY TREATED WITH CISPLATIN

U-33 TREATING VIRAL INFECTIONS IN A MAMMAL

U-34 TREATING VIRAL INFECTIONS IN A WARM-BLOODED ANIMAL

U-35 TREATING CYTOMEGALOVIRUS IN A HUMAN WITH AN INJECTABLE COMPOSITION

U-36 METHODS OF TREATING BACTERIAL ILLNESSES

U-37 METHOD OF TREATING GASTROINTESTINAL DISEASE

U-38 TREATMENT OF PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

U-39 ANGINA PECTORIS

U-40 METHOD OF TREATMENT OF BURNS

U-41 METHOD OF TREATING CARDIAC ARRHYTHMIAS

U-42 ADJUVANT TREATMENT IN COMBINATION WITH FLUOROURACIL AFTER SURGICAL RESECTION IN PATIENTS WITH DUKES' STAGE C COLON CANCER

U-43 MANAGEMENT OF CHRONIC PAIN IN PATIENTS REQUIRING OPIOID ANALGESIA

U-44 RELIEF OF NAUSEA AND VOMITING

U-45 TREATMENT OF INFLAMMATION AND ANALGESIA

U-46 TREATMENT OF PANIC DISORDER

U-47 STIMULATION OF THE RELEASE OF GROWTH HORMONE

U-48 ANALGESIA

U-49 SYMPTOMATIC CANCER-RELATED HYPERCALCEMIA

U-50 USE IN TREATING INFLAMMATORY DERMATOSES

U-51 BLOOD POOL IMAGING, INCLUDING CARDIAC FIRST PASS AND GATED EQUILIBRIUM IMAGING AND FOR DETECTION OF SITES OF GASTROINTESTINAL BLEEDING

U-52 TREATMENT OF ADULT AND PEDIATRIC PATIENTS(OVER SIX MONTHS OF AGE) WITH ADVANCED HIV INFECTION

U-53 HYPERCALCEMIA OF MALIGNANCY

U-54 REVERSAL AGENT OR ANTAGONIST OF NONDEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS

U-55 TREATMENT OF PAIN

U-56 AID TO SMOKING CESSATION

U-57 OPHTHALMIC USE OF NORFLOXACIN

U-58 METHOD OF TREATING INFLAMMATORY INTESTINAL DISEASES

U-59 METHOD OF TREATING HYPERCHOLESTEROLEMIA

U-60 NASAL ADMINISTRATION OF BUTORPHANOL

U-61 CEREBRAL AND PERIPHERAL ARTERIOGRAPHY AND CT IMAGING OF THE HEAD

U-62 CORONARY ARTERIOGRAPHY, LEFT VENTRICULOGRAPHY, CT IMAGING OF THE BODY, INTRAVENOUS EXCRETORY UROGRAPHY, INTRAVENOUS DIGITAL SUBTRACTION ANGIOGRAPHY AND VENOGRAPHY

U-63 ISOPRENALINE ANTAGONISM ON THE HEART RATE OR BLOOD PRESSURE

U-64 TREATMENT OF VIRAL INFECTIONS

U-65 METHOD OF TREATMENT OF A PATIENT INFECTED WITH HIV

U-66 TRIPHASIC REGIMEN

U-67 METHOD OF INDUCING ANESTHESIA IN A WARM BLOODED ANIMAL

U-68 TREATMENT OF ACTINIC KERATOSIS

U-69 TREATMENT OF PNEUMOCYSTIS CARINII INFECTIONS

U-70 TREATMENT OF TRANSIENT INSOMNIA

U-71 METHOD OF TREATMENT OF HEART FAILURE

U-72 TREATMENT OF MIGRAINE

U-73 METHOD OF TREATING DISEASES OR INFECTIONS CAUSED BY MYCETES

U-74 METHOD OF PROVIDING HYPNOTIC EFFECT

U-75 RELIEF OF OCULAR ITCHING DUE TO SEASONAL ALLERGIC CONJUNCTIVITIS

U-76 USE TO IMAGE A SUBJECT WITH A MAGNETIC RESONANCE IMAGING SYSTEM

U-77 TREATMENT OF SYMPTOMS OF SEASONAL ALLERGIC RHINITIS

U-78 ULCERATIVE COLITIS

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U-81 RELIEF OF SYMPTOMS ASSOCIATED WITH SEASONAL ALLERGIC RHINITIS

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U-90 TREATMENT OF PYSCHOTIC DISORDERS

U-91 ALTERNATIVE THERAPY TO TRIMETHOPRIMSULFAMETHOXAZOLE FOR TREATMENT OF MODERATE-TO-SEVERE PNEUMOCYSTIS CARINII PNEUMONIA IN IMMUNOCOMPROMISED AND AIDS PATIENTS

U-92 TREATMENT OF DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE I INSULIN DEPENDENT DIABETES MELLITUS AND RETINOPATY

U-93 USE AS AN ANTIHISTAMINE/DECONGESTANT

U-94 TREATMENT-ADULTS W/ ADVANCED HIV,INTOLERANT OF APPROVED THERAPIES,INTOLERANT OF APPROVED THERAPIES W/PROVEN BENEFIT OR HAVE EXPERIENCED CLINICAL/IMMUNOLOGICAL DETERIORATION WHILE RECEIVING..OR FOR WHOM SUCH THERAPIES-CONTRAINDICATED

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U-96 METHOD OF TREATING VARICELLA ZOSTER (SHINGLES) INFECTIONS

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U-101 ADJUNCT TO CONVENTIONAL CT OR MRI IMAGING IN THE LOCALIZATION OF STROKE IN PATIENTS IN WHOM STROKE HAS ALREADY BEEN DIAGNOSED

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U-104 TREATMENT OF AQUEOUS HUMOR FORMATION AND INTRAOCULAR PRESSURE

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U-106 TREATMENT OF EPILEPSY

U-107 TREATMENT OF HYPERTENSION AND ANGINA PECTORIS

U-108 SHORT-TERM TREATMENT OF ACTIVE DUODENAL ULCER, GASTROESOPHAGEAL REFLUX DISEASE (GERD), SEVERE EROSIVE ESOPHAGITIS, POORLY RESPONSIVE SYMPTOMATIC GERD AND PATHOLOGIAL HYPERSECRETORY CONDITIONS AND MAINTENANCE HEALING OF EROSIVE ESOPHAGITIS

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U-131 PHOTODAMAGED SKIN

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U-157 TREATMENT OF A HUMAN SUFFERING FROM VITAMIN B12 DEFICIENCY

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U-169 METHODS OF USING THE COMPOUND/DRUG PRODUCT AS A CONTRAST AGENT IN MAGNETIC RESONANCE IMAGING

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U-172 TREATMENT OF GENITAL WARTS

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U-175 METHOD OF TREATING MALIGNANT TUMORS

U-176 METHOD OF TREATING A PATIENT SUFFERING FROM LISTED CONDITIONS, INCLUDING SPECIFIC PSYCHOSES

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U-180 TREATMENT OF ADULT AND PEDIATRIC PATIENTS (OVER 6 MONTHS OF AGE) WITH ADVANCED HIV INFECTION

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U-182 USE OF SALMETEROL IN PATIENTS WITH REVERSIBLE AIRWAY OBSTRUCTION

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U-189 ENHANCEMENT OF THE BIOAVAILABILITY OF THE DRUG SUBSTANCE

U-190 USE OF RITONAVIR IN COMBINATION WITH ANY REVERSE TRANSCRIPTASE INHIBITOR

U-191 METHOD OF TREATMENT FOR CONTROLLING AND LOWERING INTRAOCULAR PRESSURE IN A HUMAN

U-192 USE IN TREATING ALLERGIC REACTIONS

U-193 PSORIASIS

U-194 TREATING ANGINA PECTORIS AND HIGH BLOOD PRESSURE

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U-199 METHOD OF TREATING INFECTIOUS UPPER GI TRACT DISORDERS CAUSED BY CAMPYLOBACTER PYLORIDIS INFECTION COMPRISING ADMINISTRATION OF A BISMUTH AGENT AND AN ANTIMICROBIAL AGENT

U-200 METHOD OF TREATING GI DISORDERS COMPRISING ADMINISTRATION OF A BISMUTH-CONTAINING AGENT AND H2 RECEPTOR BLOCKING ANTI-SECRETORY AGENT

U-201 METHOD OF TREATING GI DISORDERS COMPRISING ADMINISTRATION OF CAMPYLOBACTER-INHIBITING ANTIMICROBIAL AGENT AND H2 RECEPTOR BLOCKING ANTISECRETORY AGENT

U-202 METHOD OF TREATING PEPTIC ULCER DISEASE CAUSED BY CAMPYLOBACTER PYLORIDIS COMPRISING ORAL ADMINISTRATION OF 50 TO 5,000MG BISMUTH DAILY FOR 3-56 DAYS

U-203 TREATMENT OF ADVANCED BREAST CANCER IN POSTMENOPAUSAL WOMEN WITH DISEASE PROGRESSION FOLLOWING ANTIESTROGEN THERAPY

U-204 USE OF TAXOL IN COMBINATION WITH G-CSF FOR TREATMENT OF PATIENTS WITH AIDS-RELATED KAPOSI'S SARCOMA

U-205 METHOD FOR TREATING HEARTBURN

U-206 METHOD OF USING FSH ALONE, WITHOUT THE PRESENCE OF EXOGENEOUS LH, IN IN VITRO FERTILIZATION

U-207 USE AS NASAL SPRAY

U-208 VAGINAL ADMINISTRATION USING SPECIFIED FORMULATION

U-209 VAGINAL ADMINISTRATION OF PROGESTERONE USING SPECIFIED FORMULATION

U-210 METHOD OF TREATING CONGESTIVE HEART FAILURE

U-211 USE IN PATIENTS WITH REVERSIBLE AIRWAY OBSTRUCTION

U-212 METHOD OF TREATMENT OF PARKINSON'S DISEASE

U-213 METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING HYPERCHOLESTEROLEMIA AND METHOD FOR TREATING HYPERLIPIDEMIA

U-214 USE AS A BLOOD GLUCOSE-LOWERING AGENT

U-215 TREATMENT OF EPILEPSY TWICE DAILY. TREATING A PATIENT BY ADMINISTERING CARBAMAZEPINE IN A DOSAGE FORM CAPABLE OF MAINTAINING BLOOD CONCENTRATION FROM 4-12MCG/ML OVER 12 HOURS

U-216 TREATMENT OF ADENOCARCINOMA, INCLUDING STAGE B2-C BY ADMINISTERING AN AGONIST OF LH-RH AND FLUTAMIDE

U-217 METHOD OF PRODUCING ANESTHESIA

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U-219 TREATMENT OF PARKINSON'S DISEASE

U-220 METHOD OF DIAGNOSIS

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U-223 TREATMENT OF BACTERIAL CONJUNCTIVITIS CAUSED BY SUSCEPTIBLE STRAINS OF MICROORGANISMS

U-224 CONTROLLING INTRAOCULAR PRESSURE

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U-226 METHOD OF ENHANCING THE DISSOLUTION PROFILE OF A PHARMACEUTICAL FROM A SOLID DOSAGE FORM CONTAINING THE PHARMACEUTICAL AND SIMETHICONE

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U-229 CARDIAC INSUFFICIENCY (CONGESTIVE HEART FAILURE)

U-230 PREVENTION OF ACUTE CARDIAC ISCHEMIC EVENTS

U-231 USE IN PARKINSON'S DISEASE

U-232 METHOD OF TREATING MIGRAINE

U-233 DECREASING MORTALITY CAUSED BY CONGESTIVE HEART FAILURE

U-234 METHOD OF USING RIBAVIRIN TO TREAT VIRAL INFECTIONS IN MAMMALS

U-235 METHOD OF MODULATING TH1 AND TH2 RESPONSE IN ACTIVATED T CELLS OF A HUMAN COMPRISING ADMINISTERING RIBAVIRIN TO THE T CELLS IN A DOSAGE WHICH PROMOTES THE TH1 RESPONSE AND SUPPRESSES THE TH2 RESPONSE

U-236 TREATING MALE PATTERN BALDNESS WITH 0.05 TO 3.0MG/DAY

U-237 METHOD OF PERFORMING NMR IMAGING WITH A PATIENT COMPRISING ADMINISTERING TO THE PATIENT AN EFFECTIVE AMOUNT OF CONTRAST AGENT DISCLOSED IN THE CLAIMS

U-238 IMAGING A BODY TISSUE AND SUBJECTING TO NMR TOMOGRAPHY, ADMINISTERING

AN AMOUNT OF PHARMACEUTICAL AGENT FOR AFFECTING THE RELAXATION TIMES OF ATOMS IN BODY TISSUES UNDERGOING NMR DIAGNOSIS, WHEREBY THE IMAGE CONTRAST IN ENHANCED....

U-239 TREATING OR CONTROLLING OCULAR INFLAMATION WHICH COMPRISES TOPICALLY ADMINISTERING TO AFFECTED EYE A COMPOSITION COMPRISING AN NSAID, A POLYMERIC QUATERNARY AMMONIUM COMPOUND AND BORIC ACID

U-240 TREATMENT OF ACUTE MIGRAINE ATTACKS

U-241 FOR SHORT-TERM TREATMENT ACTIVE DUODENAL ULCER, MAINTENANCE THERAPY FOR DUODENAL ULCER PATIENTS AT REDUCED DOSAGE AFTER HEALING OF ACTIVE ULCER, SHORT-TERM TREATMENT ACTIVE BENIGN GASTRIC ULCER & GERD, PATHOLOGICAL HYPERSECRETORY CONDITIONS

U-242 USE OF FOLLITROPIN ALPHA ALONE IN IN-VITRO FERTILIZATION

U-243 TOPICAL ADMINISTRATION

U-244 PLATELET AGGREGATION INHIBITORS

U-245 TREATMENT OF SEBORRHEA DERMATITIS IN HUMANS

U-246 PHOSPHATE BINDING

U-247 TREATMENT OF RHEUMATOID ARTHRITIS

U-248 TREATMENT OF HIV

U-249 METHOD OF TREATING ALLERGIC OR NON-ALLERGIC RHINITIS IN PATIENTS BY ADMINISTERING AEROSOLIZED PARTICLES OF MOMETASONE FUROATE

U-250 TREATMENT OF HEPATITIS B INFECTION

U-251 USE OF TROGLITAZONE IN COMBINATION WITH SULFONYLUREAS IN THE TREATMENT OF TYPE II DIABETES

U-252 METHOD OF TREATING A HUMAN SUBJECT HAVING GAUCHER'S DISEASE

U-253 ORAL TRANSMUCOSAL USE

U-254 USE OF AGGRASTAT IN COMBINATION WITH HEPARIN

U-255 IMPROVED WAKEFULNESS IN PATIENTS WITH EXCESSIVE DAYTIME SLEEPINESS ASSOCIATED WITH NARCOLEPSY

U-256 TREATMENT OF HIV INFECTION IN COMBINATION WITH ONE OR MORE ADDITIONAL HIV ANTIVIRAL AGENTS

U-257 TREATMENT OF HIV INFECTION

U-258 TREATMENT OF NEURODEGENERATIVE DISEASES

U-259 TREATMENT OF ANDROGENIC ALOPECIA BY ORAL ADMINISTRATION DRUG SUBSTANCE

U-260 REDUCTION OF INTRAOCULAR PRESSURE IN PATIENTS WITH OPEN ANGLE GLAUCOMA AND OCULAR HYPERTENSION WHO ARE INTOLERANT OF OTHER IOP LOWERING MEDICATIONS OR INSUFFICIENTLY RESPONSIVE TO ANOTHER IOP LOWERING MEDICATION

U-261 TREATING BENIGN PROSTATIC HYPERPLASIA WITH A GENUS OF COMPOUNDS, INCLUDING FINASTERIDE

U-262 TREATING BENIGN PROSTATIC HYPERTROPHY WITH FINASTERIDE

U-263 METHOD OF TREATING A MALIGNANT CONDITION THROUGH INTRAVASCULAR ADMINISTRATION OF BUSULFAN. METHOD FOR TREATING LEUKEMIA OR LYMPHOMA IN A PATIENT UNDERGOING A BONE MARROW TRANSPLANT THROUGH INTRAVENOUS ADMINISTRATION OF BUSULFAN

U-264 METHOD OF TREATING A MALIGNANT DISEASE THROUGH PARENTERAL ADMINISTRATION OF BUSULFAN. METHOD FOR TREATING A PATIENT UNDERGOING A BONE MARROW TRANSPLANT THROUGH INTRAVASCULAR ADMINISTRATION OF BUSULFAN

U-265 USE AS LAXATIVE

U-266 RELIEF OF THE SIGNS AND SYMPTOMS OF OSTEOARTHRITIS; RELIEF OF THE SIGNS AND SYMPTOMS OF RHEUMATOID ARTHRITIS IN ADULTS; MANAGEMENT OF ACUTE PAIN IN ADULTS; TREATMENT OF PRIMARY DYSMENNORRHEA; ACUTE TREATMENT OF MIGRAINE ATTACKS IN ADULTS

U-267 PREVENTING HEARTBURN EPISODES FOLLOWING INGESTION OF HEARTBURN-INDUCING FOOD/BEVERAGE, COMPRISING ADMIN TO PT, 30 MIN PRIOR TO CONSUMPTION BY THE PT THE FOOD/BEVERAGE, A COMPOSITION COMPRISING 10MG FAMOTIDINE

U-268 ACROMEGALY

U-269 EXCESS GH-SECRETION OR GASTRO-INTESTINAL DISORDERS

U-270 METHOD OF IMPROVING THE TIME FOR ADMINISTRATION OR THE TIME BETWEEN CHANGES OF GIVING SETS FOR THE DRUG PRODUCT

U-271 METHOD OF TREATING TUMORS

U-272 METHOD OF TREATING CARCINOMA

U-273 CUTANEOUS T-CELL LYMPHOMA

U-274 ZANAMIVIR FOR INHALATION

U-275 METHOD OF USE OF THE DRUG SUB-STANCE

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U-489 EXPECTORANT

U-490 TESTOSTERONE REPLACEMENT THERAPY IN MALES FOR CONDITIONS ASSOCIATED WITH A DEFICIENCY OR ABSENCE OF ENDOGENOUS TESTOSTERONE

U-491 METHOD OF DELIVERING A DRUG TO THE LUNG

U-492 METHOD FOR THE TREATMENT OF SKIN, SUFFERING FROM A CONDITION SELECTED FROM A GROUP CONSISTING OF NONACNE INFLAMMATORY DERMATOSES... COMPRISING APPLYING TO AFFECTED AREA. A THERAPEUTICALLY EFFECTIVE AMT AZELAIC ACID

U-493 TREATMENT OF TYPE 2 DIABETES MELLITUS

U-494 TREATMENT OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER

U-495 PERITONEAL DIALYSIS SOLUTION

U-496 METHOD FOR TREATING CHRONIC RENAL FAILURE

U-497 RELIEF OF THE SIGNS AND SYMPTOMS OF OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS

U-498 INTRA-ARTERIAL AND INTRAVENOUS USES OF ULTRAVIST

U-499 METHOD OF USING REBETOL CAPSULES IN COMBINATION WITH A CONJUGATE COMPRISING POLYETHYLENE GLYCOL(PEG) AND AN ALPHA INTERFERON, INCLUDING, FOR EXAMPLE, PEG-INTRON POWDER FOR INJECTION

U-500 USE AS AN ANTIHYPERTENSIVE AGENT

U-501 TREATMENT OF RECURRENT HERPES LABIALIS (COLD SORES) IN ADULTS

U-502 PITYRIASIS VERSICOLOR

U-503 GENERATOR MUST BE USED WITH INFUSION SYSTEM SPECIFICALLY LABELED FOR USE WITH GENERATOR

U-504 TINEA PEDIS, TINEA CRURIS, TINEA CORPORIS

U-505 ULTRASOUND CONTRAST AGENT

U-506 PHARM PRODUCT CONTAINER 1ST CHAMBER IS DISPOSED AQUEOUS DILUENT SOL 2ND CHAMBER PHARM ACTIVE AGENT COMPRISING ACETYLCHOLINE,BUFFER IN 1ST CHAM IS SUFFICIENT TO BUFFER PH OF MIXED SOL RESULTING MIXTURE OF AQUEOUS DILUENT SOL & PHARM ACTIVE..

U-507 ACROMEGALY IN PATIENTS W/INADEQUATE RESPONSE TO SURGERY AND/OR RADIATION THERAPY AND/OR MEDICAL THERAPIES, OR FOR WHOM THESE THERAPIES ARE NOT APPROPRIATE

U-508 METHOD OF RELEASING 17-BETA OESTRADIOL PRECURSOR IN A SUBSTANTIALLY ZERO ORDER PATTERN FOR AT LEAST THREE WEEKS

U-509 TREATMENT OF CUTANEOUS MANIFESTATIONS OF CUTANEOUS T-CELL LYMPHOMA IN PATIENTS WHO ARE REFRACTORY TO AT LEAST ONE PRIOR SYSTEMIC THERAPY

U-510 TOPICAL TREATMENT OF CUTANEOUS LESIONS IN PATIENTS WITH CUTANEOUS T-CELL LYMPHOMA (STAGE IA AND IB) WHO HAVE REFRACTORY OR PERSISTENT DISEASE AFTER OTHER THERAPIES OR WHO HAVE NOT TOLERATED OTHER THERAPIES

U-511 USE OF QUINOLONE COMPOUNDS AGAINST ANAEROBIC PATHOGENIC BACTERIA

U-512 USE OF QUINOLONE COMPOUNDS AGAINST ATYPICAL UPPER RESPIRATORY PATHOGENIC BACTERIA

U-513 METHODS OF USE OF ANTIMICROBIAL COMPOUNDS AGAINST PATHOGENIC AMYCOPLASMA BACTERIA

U-514 PREVENTION OF OVULATION IN A WOMAN

U-515 TREATMENT OF MULTIPLE MYELOMA PATIENTS WHO HAVE RECEIVED AT LEAST TWO PRIOR THERAPIES AND HAVE DEMONSTRATED DISEASE PROGRESSION ON THE LAST THERAPY

U-516 METHOD OF TREATING A PSYCHOTIC DISEASE

U-517 STABLE GEL FORMULATION FOR TOPICAL TREATMENT OF SKIN CONDITIONS

U-518 OBSESSIVE COMPULSIVE DISORDER

U-519 POST OPERATIVE NAUSEA AND VOMITING

U-520 PREMENOPAUSAL OSTEOPOROSIS

U-521 METHOD OF USING RIBAVIRIN IN COMBINATION WITH INTRON A (INTERFERON ALPHA-2 B RECOMBINANT) INJECTION TO TREAT PATIENTS WITH CHRONIC HEPATITIS C

U-522 TREATMENT OF CMV RETINITIS BY INTRAVITREAL ADMIN OF A PHOSPHOROTHIOATE OLIGONUCLEOTIDE CAPABLE OF HYBRIDIZING WITH CMV MRNA

U-523 METHOD OF TREATING INFECTION BY CRYPTOSPORIDIUM PARVUM IN AN IMMUNOCOMPROMISED MAMMAL

U-524 METHOD OF TREATING DIARRHEA

U-525 METHOD OF TREATING PARASITIC INFECTIONS

U-526 METHOD OF PROVIDING CONTROLLED RELEASE OF A TREATING AGENT USING A CONTROLLED RELEASE COMPOSITION

U-527 METHOD OF DELIVERING AN ACTIVE INGREDIENT USING A PROGRESSIVE HYDRATION BIOADHESIVE

U-528 PREVENTION OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

U-529 ONCE DAILY TREATMENT OF ASTHMA WITH NEBULIZED BUDESONIDE

U-530 TREATMENT OF HERPES ZOSTER, TREATMENT OF GENITAL HERPES, TREATMENT OF COLD SORES, SUPPRESSION OF GENITAL HERPES IN IMMUNOCOPETENT AND HIV-INFECTED INDIVIDUALS, REDUCTION OF RISK OF HETEROSEXUAL TRANSMISSION OF GENITAL HERPES

U-531 TREATMENT OF PATIENTS WITH ESSENTIAL HYPERTENSION. MAY BE USED ALONE OR GIVEN WITH OTHER CLASSES OF ANTIHYPERTENSIVES, ESPECIALLY THIAZIDE DERIVATIVES

U-532 TREATMENT OF BRONCHOSPASM ASSOCIATED WITH COPD IN PATIENTS REQUIRING MORE THAN ONE BRONCHO DILATOR

U-533 ERECTILE DYSFUNCTION

U-534 HUMALOG IS AN INSULIN ANALOG THAT IS INDICATED IN THE TREATMENT OF PATIENTS WITH DIABETES MELLITUS FOR THE CONTROL OF HYPERGLYCEMIA

U-535 TREATMENT OF SOCIAL ANXIETY DISORDER

U-536 CONTRAST AGENT FOR MAGNETIC RESONACE IMAGING

U-537 TREATMENT OF CONDITIONS RELATED TO HYPERALDOSTERONISM SUCH AS HYPERTENSION AND CARDIAC INSUFFICIENCY, WITH EPLERENONE

U-538 FIRST LINE TREATMENT OF SEVERE HYPERTENSION, IN PATIENTS WITH HYPERTENSION SEVERE ENOUGH THAT THE VALUE OF ACHIEVING PROMPT BLOOD PRESSURE CONTROL EXCEEDS THE RISK OF INITIATING COMBINATION THERAPY IN THESE PATIENTS

U-539 TREATMENT OF MODERATE TO SEVERE DEMENTIA OF THE ALZHEIMER'S TYPE

U-540 TREATMENT OF FUNGAL INFECTIONS

U-541 METHOD OF TREATMENT OF ADULTS INFECTED WITH HIV-1

U-542 METHOD OF TREATING PATIENT WITH TYPE 2 DIABETES BY ONCE DAILY ADMINISTRATION

U-543 TREATMENT OF SCHIZOPHRENIA

U-544 TREATMENT OF OVERACTIVE BLADDER. TREATMENT OF URINARY INCONTINENCE.

U-545 METHOD FOR THE PREVENTION AND/OR TREATMENT OF THROMBOTIC EPISODES,

SUCH AS MYOCARDIAL INFARCTION, IN A HUMAN PATIENT AND METHOD FOR THE PREVENTION OF VENOUS THROMBOSIS IN A POSTOPERATIVE HUMAN PATIENT

U-546 USE OF REPAGLINIDE IN COMBINATION WITH METFORMIN TO LOWER BLOOD GLUCOSE

U-547 MAINTENANCE MONOTHERAPY FOR BIPOLAR DISORDER

U-548 A METHOD OF REDUCING FLUSH IN AN INDIVIDUAL BEING TREATED FOR A LIPIDEMIC DISORDER AND EFFECTIVELY TREATING THE LIPIDEMIC DISORDER

U-549 USE IN THE TREATMENT OF MEN WITH ADVANCED SYMPTOMATIC PROSTATE CANCER

U-550 TREATMENT OF BIPOLAR DISORDER AND SCHIZOPHRENIA

U-551 METHOD FOR REDUCING TOXICITY OF ALIMTA TREATED PATIENTS BY ADMINISTERING FOLIC ACID

U-552 TREATMENT OF HYPERTENSION AND HYPERLIPIDEMIA WITH A SINGLE COMPOSITION

U-553 MANAGEMENT OF PAIN AND DISCOMFORT ASSOCIATED WITH PERIDONTAL SCALING AND ROOT PLANNING PROCEDURES BY APPLICATION OF AN EUTECTIC MIXTURE OF LOCAL ANESTHETICS TO PERIDONTAL POCKETS

U-554 TREATING HIV INFECTION WITH INDINAVIR SULFATE IN COMBINATION WITH ANTIRETROVIRAL AGENTS

U-555 TREATMENT OF COMPLICATED URINARY TRACT INFECTIONS AND ACUTE UNCOMPLICATED PYELONEPHRITIS

U-556 USE AS ADJUNCT DIAGNOSTIC FOR SERUM THYROGLOBULIN (TG) TESTING

U-557 NASAL TREATMENT OF SEASONAL AND PERENNIAL ALLERGIC RHINITIS SYMPTOMS

U-558 INDICATED FOR THE RELIEF OF BRONCHOSPASM IN PATIENTS 2-12 YEARS OF AGE WITH ASTHMA (REVERSIBLE OBSTRUCTIVE AIRWAY DISEASE)

U-559 METHOD OF DECREASING OR REDUCING PARATHYROID HORMONE LEVEL; METHOD OF MODULATING PARATHYROID HORMONE SECRETION;METHOD OF TREATING HYPERPARATHYROIDISM; METHOD OF REDUCING SERUM IONIZED CALCIUM LEVEL

U-560 METHOD OF DECREASING PARATHYROID HORMONE LEVEL;METHOD OF TREATING HYPERPARATHYROIDISM

U-561 COSOPT IS INDICATED FOR THE REDUCTION OF ELEVATED INTRAOCULAR PRESSURE IN PATIENTS WITH OPEN-ANGLE GLAUCOMA OR OCULAR HYPERTENSION WHO ARE INSUFFICIENTLY RESPONSIVE TO BETA BLOCKERS

U-562 TOPICAL TREATMENT OF CUTANEOUS LESIONS IN PATIENTS WITH AIDS-RELATED KAPOSI'S SARCOMA

U-563 MARINOL IS INDICATED FOR, INTER ALIA, ANOREXIA ASSOCIATED WITH WEIGHT LOSS IN PATIENTS WITH AIDS

U-564 TREATMENT OF HIV IN CONCOMITANT THERAPY

U-565 TREATMENT OF SEASONAL AND PERENNIAL ALLERGIC RHINITIS SYMPTOMS, AND CHRONIC URTICARIA

U-566 FOR THE LONG-TERM, ONCE-DAILY, MAINTENANCE TREATMENT OF BRONCHOSPASM ASSOCIATED WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD), INCLUDING CHRONIC BRONCHITIS AND EMPHYSEMA

U-567 METHOD OF TREATING INFERTILITY

U-568 METHOD OF USING FSH ALONE (WITHOUT EXOGENOUS LH) IN IN VITRO FERTILIZATION

U-569 METHOD OF USING FSH ALONE (WITHOUT EXOGENOUS LH) IN IN VITRO FERTILIZATION AND WHEREIN THEREAFTER AN OVULATORY INDUCING AMOUNT OF HCG IS ADMINISTERED

U-570 METHOD OF USING FSH ALONE (WITHOUT EXOGENOUS LH) IN IN VITRO FERTILIZATION AND WHEREIN THE DAILY AMOUNT OF FSH IS ABOUT 5-10 IU/KG

U-571 TREATMENT OF AGITATION ASSOCIATED WITH SCHIZOPHRENIA AND BIPOLAR I MANIA

U-572 INTENSIVE CARE UNIT SEDATION

U-573 TREATMENT OF ACUTE PROMYELOGENOUS LEUKEMIA (APL)

U-574 PROPHYLAXIS AND TREATMENT OF THE NASAL SYMPTOMS OF SEASONAL ALLERGIC RHINITIS AND TREATMENT OF THE NASAL

SYMPTOMS OF PERENNIAL ALLERGIC RHINITIS IN ADULTS AND PEDIATRIC PATIENTS 12 YEARS OF AGE AND OLDER

U-575 LOTEMAX OPTHALMIC SUSPENSION IS INDICATED FOR THE TREATMENT OF STEROID RESPONSIVE CONDITIONS OF THE PALPEBRAL BULBAR CONJUNCTIVA, CORNEA AND ANTERIOR SEGMENT OF THE GLOBE.

U-576 ALREX OPTHALMIC SUSPENSION IS INDICATED FOR THE TEMPORARY RELIEF OF THE SIGNS AND SYMPTOMS OF SEASONAL ALLERGIC CONJUNCTIVITIS.

U-577 TREATMENT OF BENIGN PROSTATIC HYPERPLASIA WITH FINASTERIDE IN COMBINATION WITH DOXAZOSIN

U-578 TREATMENT OF COMMUNITY ACQUIRED PNEUMONIA, ACUTE EXACERBATION OF CHRONIC BRONCHITIS, AND ACUTE BACTERIAL SINUSITIS CAUSED BY SUSCEPTIBLE STRAINS OF DESIGNATED MICROORGANISMS IN PATIENTS 18 YEARS AND OLDER.

U-579 TREATMENT OF EPILEPSY AND/OR MIGRAINE.

U-580 TREATMENT OF DISORDERS OF THE SEROTONERGIC SYSTEM SUCH AS DEPRESSION AND ANXIETY-RELATED DISORDERS

U-581 METHOD OF TREATING A CONDITION CAPABLE OF TREATMENT BY INHALATION, E.G. ASTHMA, COMPRISING ADMINISTRATION OF A FORMULATION CLAIMED IN US PATENT NO. 6743413

U-582 METHOD FOR THE TREATMENT OF A RESPIRATORY DISORDER, E.G. ASTHMA, COMPRISING ADMINISTERING AN EFFECTIVE AMOUNT OF AN AEROSOL COMPOSITION TO A PATIENT FROM A METERED DOSE INHALER SYSTEM AS CLAIMED IN US PATENT NO. 6253762

U-583 METHOD FOR THE TREATMENT OF A RESPIRATORY DISORDER, E.G. ASTHMA, COMPRISING ADMINISTERING TO A PATIENT BY INHALATION, A METERED AEROSOL DOSE OF A DRUG FORMULATION FROM THE METERED DOSE INHALER SYSTEM CLAIMED IN US 6546928

U-584 SINGLE-DOSE ADMINISTRATION BY THE EPIDURAL ROUTE, AT THE LUMBAR LEVEL, FOR THE TREATMENT OF PAIN FOLLOWING MAJOR SURGERY

U-585 TO PROMOTE WEIGHT GAIN AFTER WEIGHT LOSS IN CERTAIN TYPES OF PATIENTS

U-586 AN INTERMEDIATE RELEASE NICOTINIC ACID FORMULATION SUITABLE FOR ORAL ADMINISTRATION ONCE-A-DAY AS A SINGLE DOSE FOR TREATING HYPERLIPIDEMIA WITHOUT CAUSING DRUG-INDUCED HEPATOTOXICITY OR ELEVATIONS IN URIC ACID OR GLUCOSE OR BOTH

U-587 USE OF EPLERENONE IN COMBINATION WITH AN ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITOR (AND OPTIONALLY A DIURETIC) FOR TREATING CONGESTIVE HEART FAILURE AND HYPERTENSION

U-588 SHORT-TERM TREATMENT OF ACTIVE DUODENAL ULCER; TREATMENT OF HEARTBURN AND OTHER SYMPTOMS ASSOCIATED WITH GERD; SHORT-TERM TREATMENT OF EROSIVE ESOPHAGITIS; MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS

U-589 METHOD FOR TREATMENT OF A RESPIRATORY DISORDER, E.G., BRONCHOSPASM, COMPRISING ADMINISTERING AN EFFECTIVE AMOUNT OF AN AEROSOL COMPOSITION TO A PATIENT FROM A METERED DOSE INHALER SYSTEM AS CLAIMED IN U.S. PATENT NO. 6131966

U-590 METHOD FOR TREATMENT OF A RESPIRATORY DISORDER,E.G.,BRONCHOSPASM,COMPRISING ADMINISTERING TO A PATIENT BY ORAL OR NASAL INHALATION A DRUG FORMULATION BY USING THE METERED DOSE INHALER SYSTEM AS CLAIMED IN US PATENT NO.6532955

U-591 TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER USING A DOSAGE FORM WHICH PROVIDES ONCE-DAILY ORAL ADMINISTRATION OF A PHENIDATE DRUG

U-592 TREATMENT OF PRIMARY HYPERCHOLESTEROLEMIA, MIXED HYPERLIPIDEMIA AND/OR HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HOFH)

U-593 TREATMENT OF PRIMARY HYPERCHOLESTEROLEMIA, MIXED HYPERLIPIDEMIA AND/OR HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HOFH)

U-594 PREVENTION OF POSTMENOPAUSAL OSTEOPOROSIS

U-595 35 MG ORALLY ONCE A WEEK FOR PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN; 35 MG ORALLY ONCE A WEEK FOR TREATMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

U-596 TREATMENT OF HORMONE RECEPTOR POSITIVE METASTATIC BREAST CANCER IN POSTMENOPAUSAL WOMEN WITH DISEASE PROGRESSION FOLLOWING ANTIESTROGEN THERAPY

U-597 FORTEO IS INDICATED FOR THE TREATMENT OF POST MENOPAUSAL WOMEN WITH OSTEOPOROSIS WHO ARE AT HIGH RISK FOR FRACTURE

U-598 PROPHYLACTIC TREATMENT OF MIGRAINE

U-599 METHOD FOR TREATING ALLERGIC CONJUNCTIVITIS

U-600 A METHOD OF TREATING A PATIENT IN NEED OF OPHTHALMIC ANTIMICROBIAL THERAPY WITH LEVOFLOXACIN

U-601 TREATMENT OF BIPOLAR DISORDER

U-602 SIGNS AND SYMPTOMS OF OSTEOARTHRITIS, RHEUMATOID ARTHRITIS IN ADULTS, AND/OR PAUCIARTICULAR OR POLYARTICULAR COURSE JUVENILE RHEUMATOID ARTHRITIS, ACUTE PAIN IN ADULTS; PRIMARY DYSMENORRHEA; AND/OR ACUTE MIGRAINE ATTACKS IN ADULTS

U-603 METHOD OF TREATING INFECTIONS COMPRISING ORALLY ADMINISTERING AN EFFECTIVE AMOUNT OF THE FDA APPROVED ORAL SUSPENSION

U-604 METHOD OF LOWERING BLOOD GLUCOSE BY ONCE DAILY ADMINISTRATION

U-605 TREATMENT OF MAJOR DEPRESSIVE DISORDER(MDD);ALTHOUGH THE MEHCHANISM OF THE ANTIDEPRESSANT ACTION OF DULOXETINE IN HUMANS IS UNKNOWN, IT IS BELIEVED TO BE RELATED TO ITS POTENTIATION OF SERATONERGIC AND NORADRENERGIC ACTIVITY IN THE CNS

U-606 USE OF IRINOTECAN IN COMBINATION WITH 5-FLUOROURACIL AND LEUCOVORIN FOR THE TREATMENT OF METASTATIC COLRECTAL CANCER

U-607 CANCIDAS IS INDICATED FOR EMPIRICAL THERAPY FOR PRESUMED FUNGAL INFECTIONS IN FEBRILE, NEUTROPENIC PATIENTS.

U-608 USE OF QUINOLONE COMPOUNDS AGAINST PNEUMOCOCCAL PATHOGENIC BACTERIA

U-609 USE OF QUINOLONE COMPOUNDS AGAINST QUINOLONE-RESISTANT PNEUMOCOCCAL PATHOGENIC BACTERIA

U-610 ATROVENT HFA (IPRATROPIUM BROMIDE HFA) INHALATION AEROSOL IS INDICATED AS A BRONCHODILATOR FOR MAINTENANCE TREATMENT OF BRONCHOSPASM ASSOCIATED WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE, INCLUDING CHRONIC BRONCHITIS AND EMPHYSEMA.

U-611 METHOD OF USING DESLORATADINE TO TREAT SEASONAL AND PERENNIAL ALLERGIC RHINITIS, PRURITIS, AND CHRONIC IDIOPATHIC URTICARIA IN PATIENTS 2 YEARS OF AGE AND OLDER

U-612 TREATMENT OF SEASONAL ALLERGY SYMPTOMS WITH NASAL CONGESTION IN ADULTS AND CHILDREN 12 YEARS OF AGE AND OLDER

U-613 REDUCTION OF SERUM PHOSPHATE

U-614 TREATMENT OF SEXUAL DYSFUNCTION

U-615 ADJUNCTIVE THERAPY TO DIET IN ADULTS TO REDUCE LDL-C, TOTAL-C, TRIGLYCERIDES AND APO B, AND INCREASE HDL-C IN PATIENTS WITH PRIMARY HYPERCHOLESTEROLEMIA OR MIXED DYSLIPIDEMIA (TYPES IIA, IIB) AND TO TREAT HYPERTRIGLYCERIDEMIA (TYPES IV, V)

U-616 MANAGEMENT OF PERSISTENT, MODERATE TO SEVERE PAIN IN PATIENTS REQUIRING CONTINUOUS, AROUND-THE-CLOCK ANALGESIA WITH A HIGH POTENCY OPIOID FOR AN EXTENDED PERIOD OF TIME GENERALLY WEEKS TO MONTHS OR LONGER

U-617 TREATMENT OF ACUTE PROMYELOGENOUS LEUKEMIA (APL)

U-618 USE OF ROSUVASTATIN CALCIUM TO REDUCE ELEVATED TOTAL-C, LDL-C, APOB, NONHDL-C OR TG LEVELS; TO INCREASE HDL-C IN ADULT PATIENTS WITH PRIMARY HYPERLIPIDEMIA OR MIXED DYSLIPIDEMIA; AND TO SLOW THE PROGRESSION OF ATHEROSCLEROSIS.

U-619 TREATMENT OF MALIGNANT NEOPLASM

U-620 TREATMENT OF INSOMNIA

U-621 METHOD OF TREATING CANCER

U-622 TREATMENT OF VEGF MEDIATED OCULAR DISEASE.

U-623 SHORT TERM TREATMENT OF ACTIVE BENIGN GASTRIC ULCER

U-624 REDUCTION OF RISK OF UPPER GASTROINTESTINAL BLEEDING IN CRITICALLY ILL PATIENTS

U-625 ALLERGIC RHINITIS OR NASAL POLYPS

U-626 CLOLAR IS INDICATED FOR THE TREATMENT OF PEDIATRIC PATIENTS 1 TO 21 YEARS OLD WITH RELAPSED OR REFRACTORY ACUTE LYMPHOBLASTIC LEUKEMIA AFTER AT LEAST TWO PRIOR REGIMENS

U-627 TREATMENT OF PATIENTS USING EXTENDED-RELEASE CARBAMAZEPINE

U-628 USE OF AVANDIA IN COMBINATION WITH A SULFONYLUREA, AND IN COMBINATION WITH METFORMIN AND A SULFONYLUREA TO IMPROVE GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

U-629 METHOD OF INDUCING A HYPNOTIC OR SEDATIVE EFFECT IN A HUMAN BY ADMINISTERING ESZOPICLONE

U-630 TREATING URINARY INCONTINENCE BY ADMINISTERING AN EXTENDED-RELEASE FORM OF DARIFENACIN

U-631 TREATING A DISEASE OF ALTERED MOTILITY OR TONE OF SMOOTH MUSCLE BY AD-

MINISTERING A MUSCARINIC RECEPTOR ANTAGONIZING AMOUNT OF DARIFENACIN

U-632 METHOD OF TREATMENT OF CANCER BY ADMINISTERING PARTICLES OF PACLITAXEL THAT HAVE A PROTEIN COATING

U-633 METHOD FOR TREATMENT OF TUMORS BY ADMINISTERING PACLITAXEL AT A DOSE IN THE RANGE OF ABOUT 30MG/METER SQUARE TO ABOUT 100MG/METER SQUARE IN A PHARMACEUTICALLY ACCEPTABLE FORMULATION THAT DOES NOT CONTAIN CREMOPHOR

U-634 METHOD FOR DELIVERY OF A BIOLOGIC (INCLUDING ANTINEOPLASTIC AGENTS) BY ADMINISTERING TO A PATIENT AN EFFECTIVE AMOUNT OF A BIOLOGIC AS A SOLID OR LIQUID WITH A POLYMERIC BIOCOMPATIBLE MATERIAL

U-635 TREATMENT OF GERD, MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS AND RISK REDUCTION OF NSAID ASSOCIATED GASTRIC ULCERS

U-636 TREATMENT OR PREVENTION OF BRONCHOSPASM OR ASTHMATIC SYMPTOMS

U-637 TREATMENT OF DIABETES WITH AN AMYLIN AGONIST

U-638 TREATMENT OF DIABETES WITH AN AMYLIN AGONIST, INCLUDING WITH INSULIN

U-639 TREATMENT OF A MAMMAL HAVING A NEED OF OR REDUCED ABILITY TO PRODUCE INSULIN WITH AN INSULIN AND AN AMYLIN SUCH AS PRAMLINTIDE

U-640 USE OF AN AMYLIN AGONIST TO REDUCE GASTRIC MOTILITY AND TREAT POST PRANDIAL HYPERGYLCEMIA

U-641 USE OF AN AMYLIN AGONIST HAVING SPECIFIED BINDING ACTIVITY TO REDUCE GASTRIC MOTILITY, INCLUDING USE THROUGH PARENTERAL ADMINISTRATION

U-642 TREATMENT AND PREVENTION OF OSTEOPOROSIS

U-643 THE SHORT TERM TREATMENT (UP TO 10 DAYS) IN PTS HAVING GASTROESOPHAGEAL REFLUX DISEASE (GERD) AS AN ALTERNATIVE TO ORAL THERAPY IN PTS WHEN THERAPY WITH NEXIUM CAPSULES IS NOT POSSIBLE OR APPROPRIATE

U-644 TREATMENT OF SEASONAL ALLERGIC RHINITIS

U-645 TREATMENT OF ASTHMA

U-646 METHOD OF TREATING OTITIS

U-647 TREATMENT OF OSTEOPOROSIS IN POST MENOPAUSAL WOMEN AND/OR THE TREATMENT TO INCREASE BONE MASS IN MEN WITH OSTEOPOROSIS

U-648 THE TREATMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN AND/OR THE TREATMENT TO INCREASE BONE MASS IN MEN

U-649 A METHOD FOR TREATING A TUMOR DISEASE

U-650 TREATMENT OF ESOPHAGEAL CANDIDIASIS AND PROPHYLAXIS OF CANDIDA INFECTIONS IN HSCT PATIENTS

U-651 TREATMENT OF ACUTE PROMYELOCYTIC LEUKEMIA (APL)

U-652 TREATMENT OF CARDIAC ARRHYTHMIA

U-653 STIMULATING INSULIN RELEASE BY ADMINISTERING EXENATIDE

U-654 LOWERING PLASMA GLUCAGON IN A SUBJECT IN NEED THEREOF, INCLUDING ONE WITH TYPE 2 DIABETES, BY ADMINISTERING AN EXEDIN OR ANALOG, SUCH AS EXENDIN-4

U-655 TREATMENT OF MILD TO MODERATE ACTIVE CHROHN'S DISEASE INVOLVING THE ILEUM AND/OR THE ASCENDING COLON AND THE MAINTENANCE OF CLINICAL REMISSION OF MILD TO MODERATE CROHN'S DISEASE INVOLVING THE ILEUM AND/OR ASCENDING COLON FOR UP TO 3 MONTHS

U-656 REDUCING GASTRIC MOTILITY OR DELAYING GASTRIC EMPTYING BY ADMINISTERING AN EXENDIN, SUCH AS EXENDIN-4

U-657 PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

U-658 TREATMENT OF ADVANCED HORMONE-DEPENDENT BREAST CANCER

U-659 TREATMENT OF LOCALLY ADVANCED OR METASTATIC NON SMALL-CELL LUNG CANCER (NSCLC) AFTER FAILURE OF AT LEAST ONE PRIOR CHEMOTHERAPY REGIMEN

U-660 TREATMENT OF HYPERTENSION AND TREATMENT OF HEART FAILURE

U-661 TREATMENT OF SEIZURE DISORDER

U-662 TREATMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

U-663 THE TREATMENT OF UNCOMPLICATED URINARY TRACT INFECTIONS

U-664 TREATMENT OF CONDITIONS FOR WHICH AN ALDOSTERONE RECEPTOR BLOCKER IS INDICATED, SUCH AS HYPERTENSION, HEART FAILURE, AND POST-MYOCARDIAL INFARCTION

U-665 METHOD OF USING THE DRUG SUBSTANCE/DRUG PRODUCT FOR ULTRASOUND IMAGING

U-666 METHOD OF TREATING ADHD

U-667 MANAGEMENT OF INCONTINENCE; METHOD FOR TREATING INCONTINENCE

U-668 LEVEMIR IS A LONG-ACTING BASAL INSULIN ANALOG THAT IS INDICATED IN THE TREATMENT OF PATIENTS WITH DIABETES MELLITUS

U-669 INDICATION OF TYPE II DIABETES

U-670 TREATMENT OF HIV-1 INFECTION BY THE CO-ADMINISTRATION OF TIPRANAVIR AND RITONAVIR.

U-671 PREVENTION AND TREATMENT OF SECONDARY HYPERPARATHYROIDISM ASSOCIATED WITH CHRONIC KIDNEY DISEASE (CKD) STAGE 3 AND 4

U-672 TREATMENT OF INFLAMMATION OR AN INFLAMMATION-ASSOCIATED DISORDER

U-673 METHOD OF TREATMENT WITH ONCE-DAILY DOSES OF 625MG/5ML

U-674 METHOD OF TREATING INSOMNIA CHARACHTERIZED BY DIFFICULTY WITH SLEEP ONSET

U-675 PROPHYLAXIS AND CHRONIC TREATMENT OF ASTHMA; RELIEF OF SYMPTOMS OF ALLERGIC RHINITIS

U-676 METHOD OF TREATING ATTENTION DEFICIT DISORDER USING ORAL ADMINISTRATION OF A BI-MODAL OR PULSATILE RELEASE COMPOSITION

U-677 A METHOD OF TREATING DISEASE AMENABLE TO TREATMENT WITH A PHENIDATE DRUG BY ONCE DAILY ORAL ADMINISTRATION OF AN EXTENDED RELEASE DOSAGE FORM

U-678 METHOD OF TREATING ATTENTION DEFICIT DISORDER AND/OR ATTENTION DEFICIT HYPERACTIVITY DISORDER

U-679 ADJUNCT TO DIET AND EXERCISE TO IMPROVE GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES WHO ARE ALREADY TREATED WITH A PIOGLITAZONE AND METFORMIN

U-680 A METHOD OF TREATING DYSLIPIDEMIA AND DYSLIPOPROTEINEMIA USING A DOSAGE FORM THAT CAN PROVIDE AN EFFECTIVE AMOUNT OF FENOFIBRATE TO A PATIENT IN A FASTED STATE WHICH IS AT LEAST 90% OF THE AUC AMOUNT PROVIDED BY THE DOSAGE FORM

U-681 TREATMENT OF PRIMARY IGF-1 DEFICIENCY

U-682 NON-BENZODIAZEPINE HYPNOTIC AGENT INDICATED FOR TREATMENT OF INSOMNIA, CHARACTERIZED BY DIFFICULTIES WITH SLEEP ONSET AND/OR SLEEP MAINTENANCE

U-683 PREVENTION OR TREATMENT OF ISCHEMIC HEART DISEASE

U-684 TREATMENT OF UNCOMPLICATED SKIN MANIFESTATIONS OF CHRONIC IDIOPATHIC URTICARIA IN ADULTS AND CHILDREN 6 YEARS OF AGE AND OLDER

U-685 EXPECTORANT AND COUGH SUPPRESSANT

U-686 EXPECTORANT AND NASAL DECONGESTANT

U-687 REDUCING FOOD INTAKE IN A SUBJECT WITH TYPE 2 DIABETES BY ADMINISTERING AN EXENDIN, SUCH AS EXENDIN-4

U-688 TREATMENT OF HIV-INFECTION IN COMBINATION WITH OTHER ANTIRETROVIRAL AGENTS

U-689 TREATMENT OF PATIENTS WITH T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA WHOSE DISEASE HAS NOT RESPONDED TO OR HAS RELAPSED FOLLOWING TREATMENT WITH AT LEAST TWO CHEMOTHERAPY REGIMENS

U-690 TO IMPROVE GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

U-691 USE AS A MONOTHERAPY, IN COMBINATION WITH A SULFONYLUREA, METFORMIN OR INSULIN OR IN COMBINATION WITH A SULFONYLUREA PLUS METFORMIN TO IMPROVE

GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

U-692 USE OF VALSARTAN TO REDUCE CARDIOVASCULAR MORTALITY IN CLINICALLY STABLE PATIENTS WITH LEFT VENTRICULAR FAILURE OR LEFT VENTRICULAR DYSFUNCTION FOLLOWING MYOCARDIAL INFARCTION

U-693 THE RECOMMENDED INITIAL DOSE OF EQUETRO IS 400MG/DAY GIVEN IN DIVIDED DOSES, TWICE DAILY. THE DOSE SHOULD BE ADJUSTED IN 200MG DAILY INCREMENTS TO ACHIEVE OPTIMAL CLINICAL RESPONSE.

U-694 LENALIDOMIDE IS AN ANALOGUE OF THALIDOMIDE. THALIDOMIDE IS A KNOWN HUMAN TERATOGEN THAT CAUSES SEVERE LIFE-THREATENING HUMAN BIRTH DEFECTS. IF LENALIDOMIDE IS TAKEN DURING PREGNANCY, IT MAY CAUSE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY.

U-695 TREATMENT OF PATIENTS WITH T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA AND T-CELL LYMPHOBLASTIC LYMPHOMA WHOSE DISEASE HAS NOT RESPONDED TO OR HAS RELAPSED FOLLOWING TREATMENT WITH AT LEAST TWO CHEMOTHERAPY REGIMENS

U-696 TREATMENT OF PATIENTS WITH T-CELL LYMPHOBLASTIC LYMPHOMA WHOSE DISEASE HAS NOT RESPONDED TO OR HAS RELAPSED FOLLOWING TREATMENT WITH AT LEAST TWO CHEMOTHERAPY REGIMENS

U-697 A METHOD OF USING RINFABATE RECOMBINANT (RHIGFBP-3) WITH MECASERMIN RECOMBINANT (RHIGF-1) TO PROMOTE LINEAR

GROWTH IN THE TRATMENT OF PRIMARY IGF-1 DEFICIENCY

U-698 METHOD OF USING ANTAGONIST OF ARGININE VASOPRESSIN (AVA) V1A AND V2 RECEPTORS FOR INTRAVENOUS TREATMENT OF PATEINTS WITH EUVOLEMIC HYPONATREMIA

U-699 NASAL TREATMENT OF SEASONAL AND PERENNIAL ALLERGIC RHINITIS SYMPTOMS

U-700 TREATMENT AND PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

U-701 TREATMENT OF HYPERCHOLESTEROLEMIA AND/OR HYPERTRIGLYCERIDEMIA

U-702 TOPICAL AEROSOL HAIR REGROWTH TREATMENT

U-703 TREATMENT OF PROTEIN KINASE RELATED DISORDERS, SUCH AS GASTROINTESTINAL STROMAL TUMOR AND RENAL CELL CARCINOMA WITH SUNITINIB

U-704 METHOD OF ADMINISTERING INSULIN VIA INHALATION

U-705 TREATING CHRONIC ANGINA BY ADMINISTERING AN EXTENDED RELEASE FORM OF RANOLAZINE

U-706 TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

U-707 ALLERGIC RHINITIS

U-708 TREATMENT OF CHRONIC NON-INFECTIOUS UVEITIS AFFECTING THE POSTERIOR SEGMENT OF THE EYE

U-709 METHOD OF COMBATING BACTERIA IN A PATIENT

U-710 A METHOD OF TREATING RESPIRATORY DISORDERS, E.G., ASTHMA, WHICH COMPRISES ADMINISTRATION BY INHALATION OF AN EFFECTIVE AMOUNT OF A PHARMACEUTICAL FORMULATION AS CLAIMED IN US PATENT NO. 5658549

U-711 ACUTE AND LONGER-TERM TREATMENT OF MAJOR DEPRESSIVE DISORDER

U-712 A METHOD OF USING A NICOTINIC ACID FORMULATION TO REDUCE ELEVATED TC, LDL-C AND TG LEVELS, AND RAISE HDL-C LEVELS IN PATIENTS WITH HYPERLIPIDEMIA

U-713 TREATMENT OF MILD TO MODERATE DEMENTIA OF THE ALZHEIMER'S TYPE

U-714 TOPICAL TREATMENT OF INTERDIGITAL TINEA PEDIS AND TINEA CORPORIS DUE TO TRICHOPHYTON RUBRUM, TRICHOPHYTON MENTAGROPHYTES OR EPIDERMOPHYTON FLOCCOSUM

U-715 FOR CLEANSING THE BOWEL IN PREPARATION FOR COLONOSCOPY, IN ADULTS 18 YEARS OF AGE OR OLDER

U-716 THE TREATMENT OR PREVENTION OF BRONCHOSPASM IN ADULTS AND CHILDREN 4 YEARS OF AGE AND OLDER WITH REVERSIBLE OBSTRUCTIVE AIRWAYS DISEASE AND THE PREVENTION OF EXERCISED-INDUCED BRONCHOSPASM IN PATIENTS 4 YEARS OF AGE AND OLDER

U-717 METHOD OF RELIEVING OR PREVENTING CONSTIPATION IN A HUMAN CONSTIPATED PATIENT

U-718 TREATMENT OF FUNGAL INFECTIONS

U-719 TREATENT OF PSYCHOSIS

U-720 TREATMENT OF NEUROLEPTIC DISEASES

U-721 TREATMENT OF INFLUENZA

U-722 PROPHYLAXIS OF INFLUENZA

U-723 PROPHYLACTIC TREATMENT OF MIGRAINE

U-724 METHOD OF TREATING SEIZURES

U-725 ALLERGIC RHINITIS AND URTICARIA

U-726 ALLERGIC RHINITIS

U-727 FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

U-728 METHOD FOR TREATING BACTERIAL INFECTION

U-729 TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD), RISK-REDUCTION OF NSAID-ASSOCIATED GASTRIC ULCER, H. PYLORI ERADICATION TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE

U-730 USE AS A NASAL SPRAY FOR TREATMENT OF THE SYMPTOMS OF SEASONAL ALLERGIC RHINITIS AND VASOMOTOR RHINITIS

U-731 USE IN COMBINATION WITH DEXAMETHASONE IS INDICATED FOR THE TREATMENT OF PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA

U-732 ACUTE TREATMENT OF THE CUTANEOUS MANIFESTATIONS OF MODERATE TO SEVERE ERYTHEMA NODOSUM LEPROSUM (ENL)

U-733 MAINTENANCE THERAPY FOR PREVENTION AND SUPRESSION OF THE CUTANEOUS MANIFESTATIONS OF ENL RECURRENCE

U-734 FIRST LINE THERAPY FOR TYPE 2 DIABETES MELLITUS

U-735 METHOD OF TREATING CHRONIC IRON OVERLOAD

U-736 METHOD FOR IONTOPHORETIC TRANSDERMAL DELIVERY OF FENTANYL HYDROCHLORIDE

U-737 DISINFECTION OF PATIENT SKIN PRIOR TO AN INVASIVE PROCEDURE

U-738 INDICATED FOR THE LONG-TERM, TWICE-DAILY MAINTENANCE TREATMENT OF ASTHMA IN PATIENTS 12 YEARS OF AGE OR OLDER

U-739 METHOD FOR TREATING CONSTIPATION BY OPENING CIC CHANNELS IN A MAMALIAN SUBJECT

U-740 FOR THE TREATMENT OF PATIENTS WITH PRIMARY BILIARY CIRRHOSIS

U-741 COMBINATION THERAPY WITH CISPLATIN FOR THE TREATMENT OF LATE STAGE CERVICAL CANCER

U-742 TWICE DAILY TOPICAL TREATMENT OF MODERATE TO SEVERE PLAQUE PSORIASIS.

U-743 ONCE A DAY TOPICAL TREATMENT OF THE INFLAMMATORY LESIONS OF ROSACEA

U-744 TREATMENT OF HIV INFECTION IN ANTIRETROVIRAL TREATMENT-EXPERIENCED ADULT PATIENTS

U-745 TREATMENT OR PREVENTION OF EMESIS

U-746 PREVENTION OR TREATMENT OF NAUSEA OR EMESIS INDUCED BY A CANCER CHEMOTHERAPEUTIC AGENT

U-747 PREVENTION OR TREATMENT OF POSTOPERATIVE NAUSEA AND VOMITING

U-748 A METHOD FOR THE TREATMENT OF A PROTEIN TYROSINE KINASE-ASSOCIATED DISORDER

U-749 METHOD OF CONTRACEPTION

U-750 TREATMENT OF HIV-1 INFECTION IN ADULTS

U-751 ONCE DAILY DOSING OF BUDESONIDE VIA NEBULIZER FOR THE TREATMENT OF ASTHMA

U-752 SUNSCREEN

U-753 AS AN ADJUNCT TO DIET AND EXERCISE TO IMPROVE GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES

U-754 USE FOR THE LONG-TERM MAINTENANCE TREATMENT OF ASTHMA

U-755 TREATMENT OF ANOREXIA, CACHEXIA, OR AN UNEXPLAINED, SIGNIFICANT WEIGHT LOSS IN PATIENTS WITH A DIAGNOSIS OF ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

U-756 ADDITION OF ONCE-WEEKLY DOSING FOR THE TREATMENT TO INCREASE BONE MASS IN MEN WITH OSTEOPOROSIS

U-757 USE AS A BILE ACID SEQUESTRANT FOR LOWERING CHOLESTEROL

U-758 TREATMENT OF SYMPTOMS OF PREMENSTRUAL DYSPHORIC DISORDER

U-759 METHOD OF USE OF ADMINISTERING LEVOTHYROXINE

U-760 PROPHYLAXIS OF INVASIVE ASPERGILLUS AND CANDIDA INFECTIONS AND TREATMENT OF OROPHARYNGEAL CANDIDAIASIS

U-761 TREATMENT OF SCHIZOPHRENIA INCLUDING MAINTAINING STABILITY IN PATIENTS WITH SCHIZOPHRENIA

U-762 TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

U-763 ADMINISTRATION OF ARIPIPRAZOLE BY INJECTION

U-764 TREATMENT OF SCHIZOPHRENIA

U-765 METHOD OF TREATING ALLERGIC CONJUNCTIVITIS

U-766 TREATMENT OF SEIZURES

U-767 MANAGEMENT OF BREAKTHROUGH PAIN IN PATIENTS WITH CANCER

U-768 A METHOD OF REDUCING THE CAPACITY OF EXTENDED RELEASE NICOTINIC ACID TO PROVOKE A FLUSHING REACTION BY PRETREATING AN INDIVIDUAL WITH A FLUSH INHIBITING AGENT PRIOR TO THE ADMINISTRATION OF THE EXTENDED RELEASE NICOTINIC ACID

U-769 REVLIMID (LENALIDOMIDE) IN COMBINATION WITH DEXAMETHASONE IS INDICATED FOR THE TREATMENT OF MULTIPLE

MYELOMA PATIENTS WHO HAVE RECEIVED AT LEASET ONE PRIOR THERAPY

U-770 LONG-TERM TREATMENT OF PATHOLOGICAL HYPERSECRETORY CONDITIONS

U-771 METHOD FOR THE TREATMENT OF DIABETES MELLITUS, SUCH AS TYPE 1 DIABETES MELLITUS OR TYPE 2 DIABETES MELITUS, IN A HUMAN PATIENT

U-772 RELIEF OF SYMPTOMS ASSOCIATED WITH SEASONAL ALLERGIC RHINITIS IN CHILDREN 2 TO 11 YEARS AND FOR THE RELIEF OF SYMPTOMS ASSOCIATED WITH UNCOMPLICATED SKIN MANIFESTATIONS OF CHRONIC IDIOPATHIC URTICARIA IN CHILDREN 6 MONTHS TO 11 YEARS

U-773 PATHOLOGICAL HYPERSECRETORY CONDITIONS

U-774 METHOD OF TREATING TYPE 2 DIABETES MELLITUS BY ADMINISTERING A DIPEPTIDYL PEPTIDASTE-IV INHIBITOR

U-775 METHOD OF TREATING TYPE 2 DIABETES MELLITUS BY ADMINISTERING A DIPEPTIDYL PEPTIDASE-IV INHIBITOR IN COMBINATION WITH METFORMIN AND/OR A SULFONYLUREA

U-776 TREATMENT OF CUTANEOUS MANIFESTATION IN PATIENTS WITH CUTANEOUS T-CELL LYMPHOMA (CTCL) WHO HAVE PROGRESSIVE, PERSISTENT OR RECURRENT DISEASE ON OR FOLLOWING TWO SYSTEMIC THERAPIES.

U-777 DECREASING MORTALITY CAUSED BY CONGESTIVE HEART FAILURE

U-778 REDUCTION OF ELEVATED INTRAOCULAR PRESSUE IN PATEINTS WITH OPEN ANGLE GLAUCOME OR OCULAR HYPERTENSION

U-779 A METHOD FOR TREATMENT OF A CANCER, WHEREIN THE CANCER IS CHRONIC MYELOGENOUS LEUKEMIA

U-780 A METHOD FOR THE TREATMENT OF CANCER

U-781 FOR TREATMENT OF ADULT PATIENTS WITH TYPE 2 DIABETES MELLITUS WHO ARE NAIVE TO PHARMACOLOGIC THERAPY

U-782 TREATMENT OF CHRONIC HEPATITIS B IN ADULT PATIENTS WITH EVIDENCE OF VIRAL REPLICATION AND EITHER EVIDENCE OF PERSISTANT ELEVATIONS IN SERUM AMINOTRANSFERASES (ALT OR AST) OR HISTOLOGICALLY ACTIVE DISEASE

U-783 DESONATE GEL IS INDICATED FOR THE TREATMENT OF MILD TO MODERATE ATOPIC DERMATITIS IN PATIENTS 3 MONTHS OF AGE AND OLDER

U-784 TREATMENT OF MODERATE TO SEVERE PRIMARY RESTLESS LEGS SYNDROME (RLS)

U-785 USE AS REPLACEMENT SOLUTION, HEMOFILTRATION SOLUTION OR HEMODIAFILTRATION SOLUTION IN CONTINUOUS RENAL REPLACEMENT THERAPY

U-786 PRODUCT IS APPROVED FOR THE TOPICAL TREATMENT OF TINEA PEDIS

U-787 MAINTENANCE TREATMENT OF ASTHMA AS PROPHYLACTIC THERAPY IN ADULT AND PEDIATRIC PATIENTS SIX YEARS OF AGE OR

OLDER, INCLUDING PATIENTS REQUIRING ORAL CORTICOSTEROID THERAPY FOR ASTHMA

U-788 METHOD OF TREATING PSYCHIATRIC SYMPTOMS ASSOCIATED WITH PREMENSTRUAL DISORDERS USING PAROXETINE

U-789 TREATMENT OF KNOWN OR SUSPECTED CYANIDE POISONING

U-790 FORTEO IS INDICATED FOR THE TREATMENT OF POST MENOPAUSAL WOMEN WITH OSTEOPOROSIS WHO ARE AT RISK FOR FRACTURE. FORTEO CAN BE USED BY PEOPLE WHO HAVE HAD A FRACTURE RELATED TO OSTEOPOROSIS

U-791 GLEEVEC IS ALSO INDICATED FOR THE TREATMENT OF PATIENTS WITH KIT (CD117) POSITIVE UNRESECTABLE AND/OR METASTATIC MALIGNANT GASTROINTESTINAL STROMAL TUMORS (GIST)

U-792 TREATMENT OF SEBORRHEA DERMATITIS IN HUMANS

U-793 FOR THE LONG TERM TREATMENT, TWICE DAILY (MORNING AND EVENING) MAINTENANCE TREATMENT OF BRONCHOCONSTRICTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD), INCLUDING CHRONIC BRONCHITIS AND EMPHYSEMA

U-794 CLOSURE OF A CLNICALLY SIGNIFICANT PATENT DUCTUS ARTERIOSUS IN PREMATURE INFANTS WEIGHING BETWEEN 500 AND 1500G, WHO ARE NO MORE THAN 32 WEEKS GESTA-

TIONAL AGE WHEN USUAL MEDICAL MANAGEMENT IS INEFFECTIVE

U-795 METHOD FOR INHIBITING NOREPINEPHRINE UPTAKE

U-796 METHOD OF TREATING DEPRESSION

U-797 METHOD OF TREATING ANXIETY

U-798 TREATMENT AND PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN BY ONCE-MONTHLY ORAL ADMINISTRATION OF IBANDRONATE SODIUM MONOHYDRATE EQUIVALENT TO 150MG OF IBANDRONIC ACID

U-799 METHOD FOR INHIBITING SEROTONIN UPTAKE

U-800 TREATMENT OF PATIENTS WITH ADVANCED OR METASTATIC BREAST CANCER WHOSE TUMORS OVEREXPRESS HER2 AND WHO HAVE RECEIVED PRIOR THERAPY INCLUDING ANTHRACYCLINE, A TAXANE AND TRASTUZUMAB

U-801 METHOD OF TREATING CANCER

U-802 METHOD OF TREATING TYPE 2 DIABETES MELLITUS BY ADMINISTERING A DIPEPTIDYL PEPTIDASE-IV INHIBITOR

U-803 METHOD OF TREATING TYPE 2 DIABETES MELLITUS BY ADMINISTERING A DIPEPTIDYL PEPTIDASE-IV INHIBITOR IN COMBINATION WITH METFORMIN

U-804 TREATMENT OF ACTINIC KERATOSES BY PHOTODYNAMIC THERAPY

U-805 TREATMENT OF IMPETIGO DUE TO STAPHYLOCOCCUS AUREUS OR STREPTOCOCCUS PYOGENES

U-806 INTRATHECAL TREATMENT OF LYMPHOMATOUS MENINGITIS

U-807 PREVENTION OF EXERCISE-INDUCED BRONCHOCONSTRICTION

U-808 THE TREATMENT OF THE SYMPTOMS OF SEASONAL AND PERENNIAL ALLERGIC RHINITIS IN PATIENTS 2 YEARS OF AGE AND OLDER

U-809 TREATMENT OF CHRONIC IDIOPATHIC URTICARIA

U-810 METHOD OF TREATMENT TO ALLEVIATE INFLAMMATION OF THE EYE

U-811 RELIEF OF SYMPTOMS ASSOCIATED WITH SEASONAL AND PERENNIAL ALLERGIC RHINITIS AND TREATMENT OF THE UNCOMPLICATED SKIN MANIFESTATIONS OF CHRONIC IDIOPATHIC URTICARIA

U-812 RELIEF OF SYMPTOMS ASSOCIATED WITH SEASONAL AND PERENNIAL ALLERGIC RHINITIS

U-813 MAINTENANCE TREATMENT OF BRONCHOCONSTRICTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

U-814 TREATMENT OF SCHIZOPHRENIA

U-815 TREATS COLD SORES/FEVER BLISTERS ON THE FACE OR LIPS. SHORTENS HEALING TIME AND DURATION OF SYMPTOMS: TINGLING, PAIN, BURNING AND/OR ITCHING

U-816 DEPRESSION, PANIC DISORDER, PREMENSTRUAL DISORDERS AND SOCIAL ANXIETY DISORDER

U-817 NASAL ADMINISTRATION OF CYANOCOBALAMIN

U-818 TOPICAL TREATMENT OF ACNE VULGARIS

U-819 MANAGEMENT OF FIBROMYALGIA

U-820 IMPROVED WAKEFULNESS IN PATIENTS WITH EXCESSIVE SLEEPINESS ASSOCIATED WITH NARCOLEPSY, OBSTRUCTIVE SLEEP APNEA/HYPOPNEA SYNDROME, AND SHIFT WORK SLEEP DISORDER

U-821 METHOD OF INHIBITING ENTHOTHELIN RECEPTORS BY ADMINISTERING AMBRISENTAN TO A PATIENT TO TREAT PULMONARY ARTERIAL HYPERTENSION.

U-822 USE IN LIPID MANAGEMENT

U-823 RELIEF OF SYMPTOMS ASSOCIATED WITH SEASONAL ALLERGIC RHINITIS AND FOR THE TREATMENT OF UNCOMPLCATED SKIN MANIFESTATIONS OF CHRONIC IDIOPATHIC URTICARIA IN CHILDREN 6 TO 11 YEARS OF AGE

U-824 METHOD OF TREATING PATIENTS INFECTED WITH CCR5-TROPIC HIV-1

U-825 USE FOR PREVENTION OF BREAST CANCER

U-826 RELIEF OF MODERATE TO SEVERE PAIN

U-827 USE FOR TREATMENT OF DIABETES, PARTICULARLY TYPE 2 DIABETES

U-828 PREVENTION OF PREGNANCY IN WOMEN WHO ELECT TO USE ORAL CONTRACEPTIVES AS A METHOD OF CONTRACEPTION

U-829 TREATMENT OF EXTRAVASATION RESULTING FROM IV ANTHRACYCLINE CHEMOTHERAPY

U-830 TREATMENT OF RELAPSED SMALL CELL LUNG CANCER

U-831 METHOD OF ADMINISTERING LANREOTIDE ACETATE

U-832 ZINGO IS INDICATED FOR THE USE ON INTACT SKIN TO PROVIDE LOCAL ANALGESIA PRIOR TO VENIPUNCTURE OR INTRAVENOUS CANNULATION.

U-833 METHOD OF TREATING PAIN USING A PHARMACEUTICALLY ACCEPTABLE SALT OF ROPIVACAINE AND ADMINISTERING A COMPOSITION CONTAINING LESS THAN 0.25% BY WEIGHT OF ROPIVACAINE

U-834 INVIRASE IN COMBINATION WITH RITONAVIR AND OTHER ANTIRETROVIRAL AGENTS IS INDICATED FOR THE TREATMENT OF HIV INFECTION

U-835 RELIEF OF THE INFLAMMATORY AND PRURITIC MANIFESTATIONS OF ATOPIC DERMATITIS IN PATIENTS ONE YEAR OF AGE OR OLDER

U-836 A METHOD FOR THE TREATMENT OF LEUKEMIAS

U-837 GASTROINTESTINAL LAVAGE INDICATED FOR CLEANSING OF THE COLON AS A PREPARATION FOR COLONOSCOPY IN ADULTS

U-838 METHOD OF TREATING PAIN USING A PHARMACEUTICALLY ACCEPTABLE SALT OF ROPIVACAINE AND ADMINISTERING A COMPOSITION CONTAINING LESS THAN 0.5% BY WEIGHT OF ROPIVACAINE

U-839 TREATMENT OF MAJOR DEPRESSIVE DISORDER (MDD)

U-840 TREATMENT FOR TYPE 2 DIABETES MELLITUS

U-841 INDICATED FOR THE LONG-TERM, MAINTENANCE TREATMENT OF ASTHMA IN PATIENTS 12 YEARS OF AGE AND OLDER

U-842 INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

U-843 METHOD FOR ADMINISTRATION OF TESTOSTERONE

U-844 PREFEST IS INDICATED IN WOMEN WHO HAVE A UTERUS FOR THE TREATMENT OF MODERATE TO SEVERE VASOMOTOR SYMPTOMS ASSOCIATED WITH MENOPAUSE; TREATMENT OF VULVAR AND VAGINAL ATROPHY; PREVENTION OF OSTEOPOROSIS

U-845 TREATMENT OF PATIENTS WITH CANDIDEMIA, ACUTE DISSEMINATED CANDIDIASIS, CANDIDA PERITONITIS AND ABCESSES

U-846 USE FOR DELINEATION (VISUALIZATION) DURING A VITRECTOMY SURGICAL PROCEDURE

U-847 ADJUNCTIVE THERAPY TO DIET IN ADULTS TO REDUCE LDL-C, TRIGLYCERIDES AND APO B, AND INCREASE HDL-C IN PA-

TIENTS WITH PRIMARY HYPERCHOLESTEROLEMIA OR MIXED DYSLIPIDEMIA (TYPES IIA, IIB) AND TO TREAT HYPERTRIGLYCERIDEMIA (TYPES IV, V)

U-848 ACUTE TREATMENT OF MIGRAINE WITH OR WITHOUT AURA

U-849 REDUCTION OF ELEVATED INTRAOCULAR PRESSURE (IOP) IN PATIENTS WITH GLAUCOMA OR OCULAR HYPERTENSION WHO REQUIRE ADJUNCTIVE OR REPLACEMENT THERAPY DUE TO INADEQUATELY CONTROLLED IOP. DOSE IS ONE DROP OF COMBIGAN IN THE AFFECTED EYE TWICE DAILY

U-850 PREVENTION OR TREATMENT OF NAUSEA OR EMESIS INDUCED BY A CANCER CHEMOTHERAPEUTIC AGENT

U-851 TREATMENT OF TYPE 2 DIABETES MELLITUS

U-852 RELIEF OF SYMPTOMS ASSOCIATED WITH SEASONAL AND PERENNIAL ALLERGIC RHINITIS

U-853 TREATMENT OR PREVENTION OF EMESIS

U-854 PREVENTION OF CMV DISEASE IN KIDNEY, HEART, AND KIDNEY-PANCREAS TRANSPLANT PATIENTS AT HIGH RISK (DONOR CMV SEROPOSITIVE/RECIPIENT CMV SERONEGATIVE)

U-855 METHOD TO INDUCE NATRIURESIS, DIURESIS AND/OR VASODILATION

U-856 SUPPORT EMBRYO IMPLANTATION AND EARLY PREGNANCY BY SUPPLEMENTATION OF CORPUS LUTEAL FUNCTION AS PART OF AN

ASSISTED REPORDUCTIVE TECHNOLOGY (ART) TREATMENT PROGRAM FOR INFERTILE WOMEN

U-857 INHIBITION OF TRANSPLANT REJECTION

U-858 PEDIATRIC USE AGED 1-11 YEARS, GERD AND EROSIVE ESOPHAGITIS

U-859 EROSIVE ESOPHAGITIS, HYPERSECRETORY CONDITIONS INCLUDING ZOLLINGER-ELLISON SYNDROME, MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS AND REDUCTION OF SYMPTOMS IN PATIENTS WITH GERD

U-860 FOR THE APPROVED USES AND CONDITIONS OF USE, INCLUDING DEPRESSION

U-861 RELIEF OF THE INFLAMMATORY AND PRURITIC MANIFESTATIONS OF CORTICOSTEROID RESPONSIVE DERMATOSES IN PATIENTS 12 YEARS OF AGE OR OLDER

U-862 ADJUNCT TO DIET TO REDUCE ELEVATED TOTAL-C, LDL-C, NON-HDL-C, APO B, TG, AND LP(A) LEVELS AND TO INCREASE HDL-C IN PATIENTS WITH PRIMARY HYPERCHOLESTEROLEMIA, MIXED DYSLIPIDEMIA, AND HYPERTRIGLYCERIDEMIA

U-863 TAKING ASPIRIN OR NON-STEROIDAL ANTI-INFLAMMATORY MEDICATIONS APPROXIMATELY 30 MINUTES BEFORE DOSING CAN MINIMIZE FLUSHING, A COMMON SIDE EFFECT OF NIACIN THERAPY

U-864 PEDIATRIC USE AGES 1-2 YEARS, GERD AND EROSIVE ESOPHAGITIS

U-865 TREATMENT OF A WOMAN WITH OSTEOPOROSIS AND A HIGH RISK FOR BONE FRACTURE BY REDUCING THE RISK OF VERTEBRAL AND NONVERTEBRAL BONE FRACTURE

U-866 THE LABEL REFERENCES THE EFFECTS OF THE ACTIVE INGREDIENT OF REVLIMID UPON CYTOKINES

U-867 TREATMENT OF MIGRAINE

U-868 METHOD OF USING ANTAGONIST OF ARGININE VASOPRESSIN (AVA) V1A AND V2 RECEPTORS FOR INTRAVENOUS TREATMENT OF PATIENTS WITH HYPERVOLEMIC HYPONATREMIA

U-869 METHOD FOR STIMULATING CORONOARY VASODILATION FOR PURPOSES OF IMAGING THE HEART

U-870 METHOD OF PRODUCING CORONARY VASODILATION WITHOUT PERIPHERAL VASODILATION

U-871 METHOD OF REDUCING RISK OF MYOCARDIAL INFARCTION, STROKE AND DEATH

U-872 TWICE DAILY MAINTENANCE TREATMENT OF AIRFLOW OBSTRUCTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD), INCLUDING CHRONIC BRONCHITIS AND EMPHYSEMA. TO REDUCE EXACERBATIONS OF COPD IN PATIENTS WITH A HISTORY OF EXACERBATIONS

U-873 METHOD OF TREATING CONSTIPATION IN A PATIENT WITH IRRITABLE BOWEL SYNDROME BY OPENING CHLORIDE CHANNELS (CIC)

U-874 METHOD OF TREATING CONSTIPATION IN A PATIENT WITH IRRITABLE BOWEL SYNDROME

U-875 FIRST-LINE TREATMENT OF LOCALLY ADVANCED UNRESECTABLE OR METASTATIC PANCREATIC CANCER

U-876 TREATMENT OF MIGRAINE WITH OR WITHOUT AURA

U-877 FOR USE AS ADJUNCTIVE THERAPY IN THE TREATMENT OF PEPTIC ULCER

U-878 A METHOD FOR BINDING A PERIPHERAL OPIOID RECEPTOR

U-879 A METHOD OF TREATING OR PREVENTING ILEUS

U-880 ENDOMETRIN IS A PROGESTERONE INDICATED TO SUPPORT EMBRYO IMPLANTATION AND EARLY PREGNANCY BY SUPPLEMENTATION OF CORPUS LUTEAL FUNCTION AS PART OF AN ASSISTED REPRODUCTIVE TECHNOLOGY (ART) TREATMENT PROGRAM FOR INFERTILE WOMEN

U-881 TREATMENT OF NON-SMALL CELL LUNG CANCER

U-882 MANAGEMENT OF FIBROMYALGIA (FM)

U-883 TREATMENT OF GASTROINTESTINAL STROMAL TUMOR WITH SUNITINIB

U-884 TREATMENT OF PATIENTS WITH MULTIPLE MYELOMA

U-885 TREATMENT OF PATIENTS WITH MANTLE CELL LYMPHOMA WHO HAVE RECEIVED AT LEAST 1 PRIOR THERAPY

U-886 ADMINISTERING DESLORATADINE TO TREAT THE SYMPTOMS OF PERENNIAL ALLERGIC RHINITIS, SEASONAL ALLERGIC RHINITIS, OR CHRONIC IDIOPATHIC URTICARIA

U-887 TREATMENT AND PREVENTION OF OSTEOPOROSIS

U-888 FEMALE HORMONE REPLACEMENT THERAPY FOR POSTMENOPAUSAL WOMEN

U-889 MENOPAUSAL AND POSTMENOPAUSAL DISORDERS (INCLUDING VASOMOTOR SYMPTOMS ASSOCCIATED WITH MENOPAUSE)

U-890 REDUCTION OF SERUM PHOSPHATE IN PATIENTS WITH END STAGE RENAL DISEASE

U-891 USE AS AN INTRAOCULAR IRRIGATING SOLUTION DURING SURGICAL PROCEDURES INVOLVING PERFUSION OF THE EYE

U-892 TREATMENT OF CUTANEOUS MANIFESTATIONS IN PATIENTS WTIH CUTANEOUS T-CELL LYMPHOMA (CTCL)

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UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

Civil Action No.: 2:05 CV 40188
Hon. Avern Cohn

EXHIBIT L TO THE DECLARATION OF DAVID L. ROSEN

* * * *

[Exhibit L Reproduced at JA 181 - 213]

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

Civil Action No.: 2:05 CV 40188
Hon. Avern Cohn

EXHIBIT M TO THE DECLARATION OF DAVID L. ROSEN

* * * *

[Exhibit M Reproduced at JA 256 - 290]

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

Civil Action No.: 2:05 CV 40188
Hon. Avern Cohn

EXHIBIT N TO THE DECLARATION OF DAVID L. ROSEN

FILED UNDER SEAL PURSUANT TO PROTECTIVE ORDER (DOCKET NO. 40)

* * * *

[Exhibit N Reproduced at JA 321 - 330]

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

Civil Action No.: 2:05 CV 40188
Hon. Avern Cohn

EXHIBIT O TO THE DECLARATION OF DAVID L. ROSEN

FILED UNDER SEAL PURSUANT TO PROTECTIVE ORDER (DOCKET NO. 40)

* * * *

[Exhibit O Reproduced at JA 331 - 339]

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

Civil Action No.: 2:05 CV 40188
Hon. Avern Cohn

EXHIBIT P TO THE DECLARATION OF DAVID L. ROSEN

FILED UNDER SEAL PURSUANT TO PROTECTIVE ORDER (DOCKET NO. 40)

* * * *

[Exhibit P Reproduced at JA 376 - 379]

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

Civil Action No.: 4:05 CV 40188
Hon. Avern Cohn

CONFIDENTIAL VIDEO DEPOSITION OF DAVID ROSEN

Washington, DC

Wednesday, September 16, 2009

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4.2 -- as set forth in 4.2b.

BY MR. CAMPBELL:

Q Are they almost identical?

A No.

Q Would you say that the claim -- or the Use Code in Exhibit 5 accurately reflects this claim?

A It's not required to reflect that claim. It's required to reflect the approved indication for use.

Q I understand that. But does the Use Code in Exhibit 5 reflects claim 4 in patent '358?

MR. WU: Objection.

THE WITNESS: It is a method for improving glycemic control. I'm not a patent lawyer, and I don't know whether or not a method for improving glycemic control would encompass a method for treating in combination.

BY MR. CAMPBELL:

Q So you have no opinion about whether or not the current Use Code describes -- accurately reflects the approved method of use of Prandin?

MR. WU: Objection.

BY MR. CAMPBELL:

Q Or strike that.

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Do you have an opinion about whether or not the Use Code in Exhibit 5 accurately reflects the method of use described in claim 4 of the '358 patent?

A I'm saying that a method of improving glycemic control in adults could encompass a method of using repaglinide in combination with metformin.

Q Okay. Does that mean, then, that that you have an opinion about whether it does or doesn't accurately reflect --

A I am not an expert in whether or not the claims of a patent are encompassed by the exact language of the -- what's in this particular Use Code. Okay? The Use Code as currently submitted here reflects the approved indication. The Use Code that was in Exhibit 6 was a reflection of the approved indication of what was in at the time the approved indication for Prandin and that the disclosures of the other parts of the

labeling include a method of improving glycemic control that includes both repaglinide alone, repaglinide in combination with metformin, and repaglinide in combination with TZDs.

MR. WU: Could you read back that answer.

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(The reporter read the record as requested.)

MR. WU: Thank you.

BY MR. CAMPBELL:

Q I want to focus on one portion of your answer there, and it's your statement that you're not an expert in whether or not claims of a patent are encompassed by a particular Use Code. Correct? That's a statement you just made; right?

A That's a statement I just made.

Q Now, it's your opinion that a NDA holder has a choice in what it describes as a -- what it provides the Use Code in 4.2b on Form 3542; right?

A It says "(submit the description of the approved indication or method of use that you propose FDA include as the 'Use Code' in the Orange Book, using no more than 240 total characters including spaces.)"

Q Okay. What I'm talking about is a -- if you can turn to Exhibit 2, which is your expert declaration in this case, which you signed -- right?

A Yes.

Q You state that "The NDA holder is given a choice between" -- strike that.

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I will slow down. If you go to paragraph 10 of your expert disclosure -- correct?

A Uh-huh.

Q If you look, the second sentence says "The NDA holder is given the choice between the 'approved indication or method of use' to utilize as its use code narrative"; right?

A That is correct.

Q And your opinion in this case is that the approved Use Code narrative -- or the Use Code narrative that Novo has chosen accurately reflects the approved indication for Prandin; correct?

A That's correct.

Q Do you have any ability -- strike that.

Do you have any expertise -- strike that.

Do you have any ability to tell me whether or not a -- the Use Code that was provided in Exhibit 5 accurately reflects the approved method of use that's covered by the '358 patent?

MR. WU: Objection.

THE WITNESS: I reviewed Section 4. --Section 4 in Exhibit 5 and where it says, you know -- it says "Does the patent claim one or more approved methods of using the approved drug?" And

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it says "Yes." And it says which claim? And it says "If the answer to 4.2 is "Yes,"' what parts of the labeling. So Novo identified parts of the labeling, okay, that cover particular claims 4. And then they went on to

provide a description of the approved indication or method of use. So they identified in Section 4.2a the portion of the approved labeling that are identified with respect to claim 4 in that particular patent.

BY MR. CAMPBELL:

Q Your opinion is that you get a choice of identifying or describing either your approved indication or your -- an approved method of use; right?

A That's correct.

Q Did Novo, when it submitted the Use Code information in Exhibit B, make that choice between those two options?

A I'm confused as to what you're referring to.

Q Okay. You get a choice of A or B; right, A being the approved indication, B be the approved method of use; right?

A And you're -- yes, there is a choice in

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Section 4.2b as to provide a description of the Use Code.

Q Right. And the Use Code can either be the approved indication or the approved method of use; correct?

A It says the approved indication or approved method of use, yes.

Q When Novo submitted its Use Code, did it do both of those?

A No.

Q Which one did it do?

A It chose to use the approved indication.

Q Okay. Now, conversely, it did not choose to describe the approved method of use; right?

A No.

Q That's not right, or is that right?

A In my view, that is not right, because it says "A method for" -- the current Use Code in Section 4.2b says "A method" -- "A method for improving glycemic control." That is broader, okay, but it covers the approved indication, and use of repaglinide in combination with metformin is a method for improving glycemic control in adults with diabetes mellitus.

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Q Your opinion is that the Use Code narrative that's included in Exhibit 5 accurately describes the approved method of use -- strike that.

It is your opinion that the Use Code included in Exhibit 5 accurately reflects the approved method of use for the '358 patent?

A I didn't say that. I said that the Use Code in Exhibit 5 accurately provides for the indication for using the product, and a method could -- a method for improving glycemic control, the use of repaglinide in combination with metformin or TZDs, both are a method for improving glycemic control in adults.

Q The Use Code that Novo submitted is more general than the claim in the '358 patent; right?

A That is correct.

Q The '358 patent -- claim 4 of the '358 patent is a subset of the Use Code provided by Novo in Exhibit 5; right?

MR. WU: Objection.

THE WITNESS: It is a method for improving glycemic control.

BY MR. CAMPBELL:

Q It's not the only method approved by FDA

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for the use of repaglinide to treat diabetes; right?

A Yes.

Q Now, the old Use Code narrative, which is in Exhibit 6, stated that "Use of repaglinide in combination with metformin to lower blood glucose"; correct?

A Yes.

Q Is there anything -- your understanding of the current indication for Prandin is that it covers -- well, strike that.

Exhibit, I believe, 7 is the current indication for Prandin; right?

A That is correct.

Q Now, is the Use Code provided in Exhibit C, the old Use Code, is there anything inaccurate about that Use Code today?

A I'm confused by your question.

Q Is there anything -- -- following -- strike that.

The Use Code that is in Exhibit 6 was in existence until May 2009 roughly; right?

A That is correct.

Q The indication that you're looking at, which is Exhibit 7, the new indication, came out in

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July of 2008; correct?

A Yes.

Q From July of 2008 up until May of 2009, was the old Use Code, in your opinion, inaccurate?

MR. WU: Objection.

THE WITNESS: No.

BY MR. CAMPBELL:

Q Okay. The old Use Code accurately described claim 4 of the '358 patent; right?

MR. WU: Objection.

THE WITNESS: The old Use Code accurately described the indication that was approved at the time for the product.

BY MR. CAMPBELL:

Q But it also accurately described the approved method of use covered by claim 4 of the '358 patent; correct?

A It's also consistent with claim 4, yes.

Q Okay. Is there a difference between "consistent with" and what I said, which is "described"?

A I don't think so, no.

Q Now, is it your understanding that the old Use Code narrative complied with FDA regulations?

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MR. WU: Objection.

THE WITNESS: FDA published the Use Code, and it was a reflection of the approved indication at the time.

BY MR. CAMPBELL:

Q Okay. It was also a reflection of the approved method of use covered by the patent; right?

MR. WU: Objection.

THE WITNESS: It was a reflection of the current indication.

BY MR. CAMPBELL:

Q It was a reflection --

A It was a reflection of the indication that was approved at the time.

Q Okay. But you also said that it was alsoconsistent with claim 4 of the patent?

A Yes, I did.

Q Let me ask you, when the FDA changed the indication, was there anything in the FDA regulations requiring Novo to change its Use Code?

A No.

Q Novo elected to do so; right?

A Yes.

Q Now, it could have maintained the old Use

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Code, even with the new indication; right?

A It could have.

Q Right. And the reason it could have is because the old Use Code accurately reflected the approved method of use claimed by the '358 patent; right?

A Yes.

Q Now I want to talk to you about the change in the FDA regulations on submission of patent information. Okay? We've already talked about that a little bit.

A Uh-huh.

Q The requirement that an NDA applicant or holder submit a Use Code narrative is a relatively new requirement; right?

A That's correct.

Q It wasn't there when you were at FDA; right?

A That is correct.

Q In fact, it's only been around since the August 2003 rulemaking that we talked about; right?

A Where the sponsor or the NDA holder would submit the use codes, that's correct.

Q Before then, the FDA would actually draft

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the Use Code based on the information provided by the NDA holder; right?

A Yes. Sometimes NDA holders actually provided that information to FDA, and FDA either would use it, or they would modify it.

Q But it wasn't required of the NDA holder to provide that Use Code?

A That is correct.

Q And now it is?

A That is correct.

Q That's one difference in the new submission requirements after August 2003; right?

A That's correct.

Q Now, in August 2003, the FDA made changes also to the type of patent information that needed to be submitted with an NDA; right?

A Yes.

Q And the new regulations required that an NDA applicant or holder submit more detailed information about use patents than previously had been required; right?

MR. WU: Objection.

THE WITNESS: It required the identification on the form of the particular claims

* * * *

[*198]

major depressive disorder by dosing at intervals of 24 hours"; right?

A Correct.

Q Now, I want to show you what's going to be marked as Exhibit 16, and this is --

(Exhibit Rosen 16 identified.)

BY MR. CAMPBELL:

Q This is the indication -- or strike that.

This is the label for the drug Aplenzin, which corresponds to U-997. Now, you can determine that, am I correct, by the first page of Exhibit 15?

A I can't determine that. I can look at the third page of Exhibit 15. And it says U-997 is associated with NDA 22108, and I can go back to the first page of 22108 or second page and say 22108 is Aplenzin, but I can get there.

Q Am I correct -- I'm not familiar with this as you are. But am I correct that I've got the proper Use Code for the proper drug indication?

A It appears that that's correct, yes.

Q As we go through this, if you see some reason why I've got this wrong, let me know. This is new to me. My understanding, though, is that this -- that you would have been told by Gibson,

[*199]

Dunn -- strike that.

You would have been provided by Gibson, Dunn this Use Code narrative in Exhibit 15, and you also would have been provided by Gibson, Dunn the indication in Exhibit 16 that appears on page 3?

A Correct.

Q Right? Now, the indication that appears on page 3 states "APLENZIN is indicated for the treatment of major depressive disorder"; right?

A Correct.

Q Now, the Use Code states that the treatment of major depressive order by dosing at intervals of 24 hours; right?

A Correct.

Q So the Use Code is more specific than the indication as it appears here; right?

A Correct.

Q Let me show you what is going to be marked as Exhibit 17.

(Exhibit Rosen 17 identified.)

BY MR. CAMPBELL:

Q Can you tell me what Exhibit 17 is?

A It appears to be a copy of U.S. patent 7,569,610.

[*200]

Q Okay. And am I correct that this is the patent that is listed for Aplenzin?

A Yes. This is one of three patents that is listed for Aplenzin that is associated with Use Code U 9-997.

Q Right. If you turn to, I believe it is, page 4 of Exhibit 15, that's where you determined that; right?

A Yes.

Q What it says there is it says that patent number 7569611 has a patent Use Code corresponding to it of U-997; right?

A That's correct.

Q So I want to take a look at the claims in that patent, the '610 patent. Okay?

A As I said before, I'm not a patent attorney, and at this point in time I would be calling a patent attorney and saying you need to come and help me and show me -- help me understand the claims of this patent, and together, we can look at how these claims interrelate with the approved labeling of the product.

Q This is why I have Rob here, for me, on my side. If you can take a look at the last page on

[*201]

this patent. Okay?

A So the back page of this patent.

Q Yes. It says -- in the right-hand column, it says "We claim"; right?

A I guess you're looking at the next-to-the-last page.

MR. WU: No, no, down here (indicating).

MR. CAMPBELL: I'm sorry.

THE WITNESS: That's why I -- okay. I see.

BY MR. CAMPBELL:

Q It says -- first, we will start with claim 1. "A method of treating depression, comprising administering an effective amount of bupropion hydrobromide to treat depression to a subject in need thereof"; right?

A That's what I see, yes.

Q If you go to claim 3, it says "The method according to claim 1, wherein said method comprises administration of a once-daily dosage of bupropion hydrobromide"; right?

A That is correct.

Q Now, am I correct that the Use Code that is identified in Exhibit 15 corresponds to the

[*202]

method-of-use patent listed in '617 -- or '610 -- strike that.

Am I correct that the Use Code identified in Exhibit 15 accurately reflects the patented method of use claimed in the '610 patent?

MR. WU: Objection.

THE WITNESS: As I said, I am not a patent attorney, and I've never held myself out to be a patent attorney. What is described in U-997 appears to be covered in the claims of the two claims that you cited.

BY MR. CAMPBELL:

Q In fact, am I correct that -- am I correct that the Use Code in 997 refers to dosing at intervals of 24 hours; right?

A Yes, it does.

Q The indication does not have that specific reference; right?

A It does not

Q The patent does have that specific reference in claim 3; correct?

MR. WU: Objection.

THE WITNESS: It appears that the patent does talk about a once-daily dosage.

[*203]

BY MR. CAMPBELL:

Q And once daily would be intervals of 24 hours; right?

MR. WU: Objection.

THE WITNESS: It's generally thought -- to be intervals of 24 hours.

BY MR. CAMPBELL:

Q Okay. Is it fair to say that the Use Code corresponds closer to the method of use claimed in the '610 patent than the indication for the drug Aplenzin?

A It is fair to say that the method of Use Code reflects the approved indications, as well as other sections of the labeling of the product.

Q I'm not sure I followed that, because you used the term "method of Use Code."

A Oh, the Use Code narrative, okay, covers both what is covered in the indications and usage, as indicated for the treatment of major depressive disorder, and they put something else in there.

Q They were more specific in the Use Code than they were in the indication; right?

A They added something else to the description of what was likely provided in Section

[*204]

4.2b.

Q Okay. And that specificity more closely resembles or corresponds to claim 3 in the '610 patent; right?

MR. WU: Objection.

THE WITNESS: That specificity includes the 24-hour or the once-daily dosage.

BY MR. CAMPBELL:

Q Okay. So am I correct that this is an example in which the Use Code corresponds to the approved method of use claimed by the patent?

MR. WU: Objection.

THE WITNESS: The Use Code is a description of the approved uses of the product.

BY MR. CAMPBELL:

Q And its a description of the approved method of use covered by the patent as well, isn't it?

MR. WU: Objection.

THE WITNESS: I don't know what their Form 3542 form said with respect to this.

BY MR. CAMPBELL:

Q I'm not asking that question. I'm asking whether the '610 patent I just showed you claims the

[*205]

method of use described in the Use Code.

A As I said, I'm not a patent expert, and I'm not going to interpret what the scope of the claims cover.

Q So are you telling me, though, that you can't provide any opinion whatsoever about the scope of patent claims and their relation to the use codes?

A I'm saying I usually have a patent attorney sitting right next to me, and he's providing me with additional information on the scope of the coverage of the patent claims. And together, with them, we come to a conclusion when I have advice and counsel from patent counsel sitting by my side.

Q Did you have patent counsel sitting by your side when you drafted or revised the declarations you submitted in connection with this case?

A No, I did not.

Q Have you consulted with patent counsel in connection with forming your opinions in this case?

A No, I have not.

Q Now, I promised to talk about those three

[*206]

examples. Now I want to actually talk about those. The first one --

A Can I get rid of this example?

Q Sure, that example you can put aside. I actually think you can move everything off if you want to clear the deck.

A I like to have my declaration and expert statement in front of me. That's what I have here.

Q That's fine. I was trying to help out.

A I appreciate that.

Q I want to talk about the original Prandin Use Code that you referred to in your supplemental declaration.

A Which original Prandin Use Code?

Q The very first Prandin Use Code that was created by the FDA in 1997.

A U-214? Is that what you're talking about?

Q Let me take a look at your declaration and refer you to the reference. Paragraph 34, page 10 of your supplemental declaration, you state that "214 use code created by the FDA for PRANDIN underscores the limited purpose for use codes"?

A Uh-huh.

Q This Use Code was created before the

[*207]

change in August 2003 and the regulations governing the submission of patent information; correct?

A That's correct.

Q This was submitted under the old regime in which the FDA itself would craft the Use Code language; correct?

A The FDA evaluated patent information that was submitted by the applicant and crafted a Use Code, yes.

Q Do you recall what the purpose was for FDA to publish a Use Code that it crafted itself?

A The purpose that the FDA publishes all this information, to provide NDA applicants with notice that there is a patent that covers a particular use or approved indication for the product.

Q What is your understanding of why FDA moved from crafting the FDA -- strike that.

What is your understanding of why FDA moved from creating the Use Code itself to requiring that NDA holders provide the exact Use Code to be included in the Orange Book?

MR. WU: Objection.

THE WITNESS: I think they've set forth

[*208]

that in the Federal Register notice that we talked about earlier today, but it's that the FDA lacks the expertise in that situation, they're short of resources, and they probably are trying to make it a little easier on themselves.

BY MR. CAMPBELL:

Q And when you say "lack of expertise," the lack of expertise in terms of interpreting the scope of patents; right?

A That's correct.

Q Now, would it be fair to say that the example of the Use Code 214 is an example that doesn't apply to the current regime? Strike that.

Would it be fair to say that the example of the Use Code 214 doesn't apply to the current regulatory regime since August of 2003?

MR. WU: Objection.

THE WITNESS: I think it shows that FDA thought that the appropriate Use Code for this product was use as a blood-glucose-lowering agent, and there were two approved uses, one in monotherapy and one in combination with metformin, and the FDA itself crafted a general Use Code used as a blood-glucose-lowering agent. So I think it set the

[*209]

stage for what FDA's expectations were, at least in this particular situation.

BY MR. CAMPBELL:

Q Now, your opinion is based on the conclusion that the -- strike that.

The Use Code 214 was to describe the patented method of uses claimed by the '924 patent; correct?

A That's my understanding. I don't believe I've looked at the '924 patent.

Q You make the statement in your initial expert declaration, in paragraph 18, that the '924 patent contained a method-of-use claim directed only to the use of repaglinide in monotherapy.

Do you see that?

A Excuse me. Which exhibit are you looking at?

Q This is Exhibit 1. It's page 6, paragraph 18. It's a good thing you kept those in front of you.

A I see that statement, yes.

Q Now, have you seen the '924 patent?

A Not that I recall.

Q Okay. So what is the basis for your

[*210]

opinion that the '924 patent contained a method-of-use claim directed only to the use of repaglinide in monotherapy?

A I believe I was given that information from counsel at Gibson, Dunn.

Q You didn't confirm that information?

A Not by reviewing the '924 patent.

Q Did you go to -- I'm sorry if I cut you off.

A No.

Q Did you go to patent counsel at your own firm to confirm the accuracy of that statement?

A No, I did not.

Q Did you do anything to confirm the accuracy of that statement?

A I just looked at the Orange Book entry.

Q And the Orange Book entry wouldn't tell you whether or not the '924 patent contained a method-of-use claim directed only to the use of repaglinide in monotherapy, would it?

A No, it would not.

Q Now, would your conclusion that the U-214 Use Code is an example of a situation where --strike that.

[*211]

Can you explain to me what you think the Use Code 214 is an example of?

MR. WU: Objection.

THE WITNESS: It's an example of the -- a general statement of the use of the product.

BY MR. CAMPBELL:

Q Okay. Am I correct in interpreting your declaration as saying, in that situation, the FDA included a Use Code that was broader than the claims covered by the listed patent?

MR. WU: Objection.

THE WITNESS: The FDA created a Use Code that reflected the approved use of the product, and I don't know if it -- I don't know what was submitted by Novo Nordisk with respect to what the scope of that patent covered.

BY MR. CAMPBELL:

Q Okay. So you can't -- now, you did represent in your expert opinion, of course, that the '924 patent only covered one of the two approved methods of use; right?

A That's correct.

Q Now, if the '924 patent actually covered both approved methods of use, would I be correct in

[*212]

concluding that the Use Code that FDA drafted accurately reflected the approved methods of use covered by the '924 patent?

MR. WU: Objection.

THE WITNESS: The Use Code provides information on the approved use of the product. It doesn't necessarily have to accurately reflect the use codes covered by the patent. That's -- now that's a standard that was in place since 2003. I don't know what Novo Nordisk submitted with respect to the listing of the '924 patent. I haven't reviewed that.

BY MR. CAMPBELL:

Q What do you know about the '924 patent?

A What I was told by Gibson, Dunn.

Q Okay. And is it anything more than that statement that I read, "The '924 patent contained a method of use claim directed only to the use of repaglinide in monotherapy"?

A That's what I know about the '924 patent, that's correct.

Q Okay. Would your conclusion change if that statement was inaccurate?

MR. WU: Objection. Which conclusion?

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THE WITNESS: Again, could you re-phrase your question or repeat your question?

BY MR. CAMPBELL:

Q Sure. Would your conclusion change if the '924 patent included all approved methods of use of repaglinide?

MR. WU: Same objection.

THE WITNESS: Would my opinion with respect to whether or not that Use Code was appropriate?

BY MR. CAMPBELL:

Q Would your opinion with respect to whether or not the Use Code 214 confirms your interpretation of the requirements of Form 3542 change if the '924 patent covered all of the approved methods of use of repaglinide?

A But 3542 wasn't in time when this patent was listed in the Orange Book. So I can't come to a conclusion in that regard without looking at that and without looking at what was actually submitted by them. But that was in 1997, and this is -- we would have to look at 2003 going forward.

Q Am I wrong? My understanding was that you cited Use Code 214 because you said the Use Code

[*214]

provided in 214 confirmed your interpretation of the requirements of Form 3542.

MR. WU: Objection.

THE WITNESS: I don't believe I said that. I think I said that I cited that U-214 was an example of the tracking of the use of the product.

BY MR. CAMPBELL:

Q Is it an example of the tracking of the method of use claimed by the patent?

A I don't -- no. I think it's a method of looking at the approved indication, track the approved indication of the patent.

Q Did it track the approved method of use claimed by the patent?

A I didn't look at the patent.

Q So you have no idea whether or not it tracks the approved method of use in the '924 patent?

A Only what was represented to me by Gibson, Dunn in this regard.

Q And what did Gibson, Dunn represent to you in this regard?

A That the '924 contained a method of use related to repaglinide in monotherapy.

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Q But not the use of repaglinide in combination with something else?

A That's correct. Either I'm going to need a little break -- or are we getting close to the end? Where are we here?

Q Let's take a very quick break, if we can. I'm hoping that we can finish up about 8:30, if that's okay.

VIDEO OPERATOR: The time is 7:48:53. Off the record.

(Recess.)

VIDEO OPERATOR: On the record. The time is 7:57:39.

BY MR. CAMPBELL:

Q Before the break, I was talking about the old branded Use Code that you referred to in your supplemental declaration; right?

A Yes.

Q I want to talk about the two other use codes you specifically referenced in your declaration, that is, the Use Code relating to the drug Starlix and the Use Code relating to Glucovance.

Do you recall that?

[*216]

A Yes.

Q I may be able to short-circuit this. Let me just ask you, did you look at the patents that are listed for those two drugs?

A No, I did not.

Q Would it be fair to say that you don't have any knowledge one way or the other whether or not the patents contain methods of use that claim the -- strike that.

Do you know whether the methods of use claimed in those listed patents cover the approved indication?

A I know what -- the use codes that have been associated with that claim from looking at the use codes and looking at the indications, but I didn't look at the specific patents. But I would presume that because they were submitted by Bristol, as well as Novartis, that they have competent people evaluating

and looking at submitting Forms 3542 with respect to those products.

Q I'm not asking whether or not their forms are inaccurate. What I'm asking is whether or not the Use Code for those drugs corresponds to the method-of-use claims listed in the Orange Book for

[*217]

those drugs.

A I know that the use codes correspond with the labeling. Okay?

Q Let me see if I can simplify this. It's late. Let me see if I can get through this. You know that the use codes correspond with the approved indications?

A Yes.

Q You don't know whether or not the use codes correspond with the approved methods of use claimed by the patents listed in the Orange Book?

A That's correct, because I did not review those patents.

Q I want to show you just a couple more documents. This is going to be marked, I believe, as Exhibit 18.

(Exhibit Rosen 18 identified.)

BY MR. CAMPBELL:

Q Do you recognize this document?

A Yes.

Q Did you review it in connection with reaching your opinions in this case?

A Yes.

Q And what is this document?

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A It's the transmission of -- dated May 6 of the amended Use Code information.

Q It's a cover letter for the Exhibit 5 that we've already marked; right?

A It's the cover letter and the Form 3542, yes.

Q Now, I want to read two portions of this. The first, this letter starts off with "In accordance with Section 314.53(c) and (d) of FDA regulations"; correct?

A That's correct.

Q Is it fair for me to say that Novo, when it submitted its May 2009 Form 3542, did so at least according to this cover letter in accordance with Section 314.53(c) and (d)?

MR. WU: Objection.

THE WITNESS: Well, it says "In accordance with" these two sections. So one would presume they submitted it in accordance with those two sections of the regulations they reference in the cover letter.

BY MR. CAMPBELL:

Q I want to talk about the second sentence in this cover letter. It says "The information

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being submitted is to amend the use code relating to U.S. Patent No. 6,677,358 to correspond with the change in labeling required by FDA in November 28, 2007 (and to correct an unrelated inadvertent error in the original Form 3542)."

Do you see that?

A Yes.

Q Okay. Now, what this refers to is that in November 2007, FDA decided that separate indications for each of the approved uses should be eliminated and a single approved indication should replace the separate indications; correct?

A Correct.

Q Now, FDA approved Novo's new merged indication for Prandin in July 2008?

A That's correct.

Q So in this letter Novo claims that the new Use Code is intended to conform with the new Prandin indication?

A To correspond with the change in labeling required by the FDA.

Q The change in labeling was the new Prandin merged indication; correct?

A The class labeling for all antidiabetic

[*220]

drugs to make sure they're all consistent.

Q You agree that Novo is not required to conform its Use Code to the approved indication in its label?

MR. WU: Objection.

THE WITNESS: Novo was required to -- could utilize either the approved use of the product or an approved method of use.

BY MR. CAMPBELL:

Q But it doesn't have to describe the approved indication; right?

A It can describe the approved indication or the approved method of use.

Q And which means that it doesn't have to describe the approved indication; right?

A It has a choice.

Q Right. And the choice could be I'm not going to provide the approved indication; right?

A It could be that they could use either the approved indication or the approved method of use.

Q Is there anything confusing about my question? I'm not sure why --

A No. I'm just saying that you've got a choice.

[*221]

Q Right. And one of the choices would be -- and given that choice, it means you don't have to do one of them?

A You can do one or the other.

Q Right. You don't have to do both?

A That's correct.

Q Novo had the option of listing either the approved indication for Prandin or a method of use claimed by the '358 patent; right?

A Or an approved method of use of the product.

Q Okay. Now, nothing in the '358 patent -- strike that.

The FDA did not ask Novo to change the Use Code, did it?

A No. But it was discussed with FDA, from my understanding.

Q Okay. Did FDA ask in those discussions Novo to change the Use Code?

A I don't believe that they asked them to change the Use Code, but the FDA asked what the Use Code was.

Q Okay. You mentioned that the FDA -- you mentioned that there were discussions between Novo

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UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

Civil Action No.: 2:05 CV 40188
Hon. Avern Cohn

DECLARATION OF DAVID S. BLOCH IN SUPPORT OF CARACO'S REPLY MEMORANDUM OF LAW IN SUPPORT OF ITS MOTION FOR SUMMARY JUDGMENT ON COUNT IV OF ITS THIRD AMENDED COUNTERCLAIMS AND SIXTH AFFIRMATIVE DEFENSE FOR PATENT MISUSE

I, David S. Bloch, declare:

1. I am an attorney at law duly licensed to practice before all the Courts of the State of California and the District of Columbia, and a member in good standing of the Bar of the United States District Court for the Eastern District of Michigan. I am a partner with the law firm of Winston & Strawn LLP, counsel of record in this matter for defendants Caraco Pharmaceutical Laboratories, Ltd., and Sun Pharmaceutical Industries, Ltd.

2. Exhibit A is a true and correct copy of Novo's May 6, 2009, amended FDA Form 3542 submission. This document has been designated "Highly Confidential" by Novo and will be submitted under seal.

3. Exhibit B is a demonstrative showing how use code narratives discussed in detail in Mr. Rosen's declaration in fact comport with the referenced method patents.

4. Exhibit C is a true and correct copy of an email exchange between Caraco's counsel and Novo's counsel, in which Novo refuses to allow Caraco to share its characterization of meetings with FDA with the FDA personnel identified in Novo's filings.

5. Exhibit D is a true and correct copy of excerpts of the rough transcript of the deposition of David Rosen, taken September 16, 2009.

I declare pursuant to 28 U.S.C. § 1746 that the foregoing is true and correct.

Executed in San Francisco, California

Dated: September 17, 2009

s/ David S. Bloch
David S. Bloch
WINSTON & STRAWN LLP
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San Francisco, CA 94111-5894
dbloch@winston.com

* * * *

[Certificate of Service and Index of Exhibits Omitted]

* * * *

EXHIBIT B

Each Use Code Example Cited in the Rosen Declaration Describes the Approved Method of Use *Claimed* by the Orange Book Listed Patent

Orange Book Listed Drug	Method of Use Claimed by the Orange Book Listed Patent	Use Code	Indication
Prandin®	Claim 1 of U.S. Patent No. 5,312,924 claims: "A method of **lowering the level of glucose in the blood** of a warm blooded animal and humans in need thereof..."	U-214 – Use as a **blood glucose-lowering agent.**	Prandin is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with type 2 diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled satisfactorily by diet and exercise alone
Starlix®	Claim 9 of U.S. Patent No. 6,559,188 claims: "The composition according to claim 1 which is **used to treat diabetes.**" Claim 10 claims: "The composition according to claim 9 wherein the **diabetes is type 2 diabetes**"	U-827 – Use for **treatment of diabetes,** particularly type 2 **diabetes.**	Starlix (nateglinide) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Glucovance®	Claim 9 of U.S Patent No. 6,303,146 claims: "A method for **treating non-insulin dependent diabetes** or hyperglycaemia, comprising **administering to a subject in need** thereof, the composition of claim 1."	U-412 – **Treatment of type 2 diabetes**	Glucovance (Glyburide and metformin HCl) tablets is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants.

Civil Action No.: 05-40188
Hon. Avern Cohn

FINAL PRETRIAL CONFERENCE

Wednesday, September 23, 2009

* * * *

[Appearances omitted]

[*2]

Detroit, Michigan

Wednesday, September 23, 2009

1:35 p.m.

MR. KLEIN: Charles Klein, Winston & Strawn, for Defendant Caraco and Defendant Sun.

MR. WITUS: Morley Witus of Barris, Sott, Denn & Driker for defendants.

MR. HSU: John Hsu from Winston & Strawn for defendants.

MR. SITZMAN: Mike Sitzman on behalf of the plaintiffs, Novo Nordisk, Inc. and Novo Nordisk A/S.

MR. BARSKY: Wayne Barsky, Gibson Dunn, also on behalf of the plaintiff, Novo Nordisk. B-a-r-s-k-y.

MS. ALAMO: Michelle Alamo, Dickinson Wright, also on behalf of plaintiffs.

THE COURT: Okay. This is a Hatch-Waxman patent case set for trial October 14th. The background of the case is reflected in reported decisions at 450 F.Supp 757 and 2009 West Law 2768955.

The parties have just finished the final pretrial conference and submitted to the Court their witness lists, exhibit lists, proposed verdict forms. If either party wants anything else from the pretrial conference memorialized, they should say so at this time.

[*3]

MR. BARSKY: Only that the Court indicated respectfully that we would have an opportunity for surrebuttal at trial if appropriate.

MR. KLEIN: Nothing to add, Your Honor.

THE COURT: Okay.

MR. KLEIN: Although, I'm sorry, we may want to add your order with regard to vacating the protective order.

THE COURT: Okay. There is a protective order in effect in this case dated October 13th, 2006, Document 40. The Court is vacating the protective order prospectively as of this date. A formal order will be entered memorializing this.

There are two motions pending before the Court. One is plaintiff's motion for partial summary judg-

ment on defendants' claims of inequitable conduct. The Court will deny the motion and will issue a memorandum explaining its reasons shortly. Particularly, since the motion is directed to only one of several acts of inequitable conduct as alleged by defendant and other alleged acts of inequitable conduct are still in the case, prudence suggests that the Court deal with inequitable conduct as a whole, but the reasons will be explained shortly.

The second motion pending before the Court is Caraco's motion for summary judgment on Count 4 of its third amended counterclaim and sixth affirmative defense for

[*4]

patent misuse. Caraco is challenging an alleged incorrect use code narrative. The Court is going to grant that motion and ask that Caraco promptly submit the form of mandatory injunctive order it thinks appropriate in the circumstances on notice to Novo. The Court is satisfied that Novo has improperly filed with the FDA for listing in the orange book the use code narrative for the method of use of Claim 4 of its '368 patent.

With the mandatory injunction in place, if Novo wants to, they can take it immediately to the Federal Circuit, but that will not affect the course of the case because the issue of the use code narrative is collateral to the issues involved in the patent litigation. A memorandum explaining the Court's reasons will be released shortly. Thank you.

MR. SITZMAN: Your Honor, can I be heard on the last motion?

THE COURT: Yeah.

MR. SITZMAN: First of all, a point of clarification just so I understand it. Is the Court granting both the summary judgment as to the patent misuse?

THE COURT: No, the patent misuse is not discussed.

MR. SITZMAN: So it's only as to the counterclaim?

THE COURT: As to the counterclaim and the request

[*5]

for an order requiring Caraco to change the use code narrative.

MR. BARSKY: So, Your Honor, the motion is going to be denied as to the misuse claim?

THE COURT: No, it's not even mentioned.

MR. BARSKY: Okay. Thank you. Your Honor -- oh, I'm sorry.

MR. SITZMAN: Two quick

THE COURT: By the way -- off the record.

(Discussion held off the record.)

THE COURT: Go ahead.

MR. SITZMAN: Thank you, Your Honor.

THE COURT: Don't interrupt each other, that's all.

MR. SITZMAN: On the use code -- on the order, I realize we are going to see the memorandum and opinion, the mandatory injunction, we would like the opportunity to request a stay from the Court, from this

Court to stay that mandatory injunction so that we can go seek relief from the Federal Circuit.

THE COURT: Well, as a practical matter I'll stay it for 20 days. That's all.

MR. SITZMAN: Okay.

THE COURT: You know, I don't know what they are going to do with the order. They are going to go to the

[*6]

FDA, I suppose, and say see what we told you.

MR. SITZMAN: And, Your Honor, just to clarify that, if we can have 20 days from the entry of the order so that we can have the order in hand to go to the Federal Circuit --

THE COURT: Sure, sure.

MR. SITZMAN: Thank you, Your Honor.

THE COURT: Again, off the record.

(Discussion held off the record.)

MR. SITZMAN: I guess the one question I have, and I appreciate the Court's comments, I will look forward to seeing the order, but you say that it's collateral to the issues that we are dealing with. Caraco's reply brief is very clear on this, that they believe that this issue mooted the order -- I'm sorry, mooted the validity trial. As I understand Caraco's theory and what the practicality is is that if the use code gets changed and they get the relief that they expect or want from the FDA, they believe that infringement is a, a fait accompli, something that they will be able to quickly establish through summary judgment and moot any reason for moving forward with a validity

trial, which would be an expensive, time-consuming event. That's how I read their argument. That's certainly what we have heard and seen from them, and it seems to me that we are on the heels of going forward with this validity trial. If

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that is the case, then we should not be going forward with this validity trial if that's where we are going in terms of infringement.

THE COURT: I'm not going to respond to that. I don't think I'm obligated to.

MR. KLEIN: Would you like me to respond to it?

THE COURT: I didn't ask you to.

MR. KLEIN: Okay.

THE COURT: I'm going to issue the order. If anyone thinks it has some effect on the trial, they can move. I don't see it having any effect because even with the old, the former use code in place, there is still a question of patent infringement and they may think it important that the validity of the patent be adjudicated. I did not ask them where they stand with the FDA so I don't know anything about that, and so you folks do whatever you want.

MR. SITZMAN: Well --

THE COURT: I'm not giving you any advice, sir. You are a good lawyer. You know what your position should be, is, and what you would like, and I was given a motion and I made the observation that I thought it was collateral. That was just an observation, that's not a ruling, but I am not going to delay the trial or anything else.

MR. SITZMAN: I think -- Your Honor, by the way,

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thank you for your comments, and I appreciate the fact that you did at least share your thoughts. I think that we have to address this maybe with counsel first and then present it to the Court, but I think that this issue has to be dealt with because if, if it is not collateral or there is a reason to vacate the trial, I don't want the Court or counsel to unnecessarily prepare for a validity trial that is either unnecessary or moot as a result of the use code decision.

THE COURT: In all candor, Mr. Sitzman, I think you are talking to the record. You are not talking to the judge. I don't mean any discourtesy. Whatever your observations or thoughts are, you can articulate them to whoever you want. All I said is I am entering two orders, one denying the motion for summary judgment, and I'll explain, and one granting the motion for the order requiring change in the use code, and I'll explain, and we have got a trial scheduled for October 14th. That's how this record stands.

MR. SITZMAN: Thank you, Your Honor.

THE COURT: Do you have anything?

MR. KLEIN: You didn't ask me to add anything, so I won't. I have nothing to volunteer.

THE COURT: Okay. Thank you. I appreciate all of your efforts today.

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(Proceedings concluded at 1:47 p.m.)

* * * *

[Certification Omitted]

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

UNITED STATES OF AMERICA
Plaintiff,

v.

All articles of drug, including active and inactive pharmaceutical components and in-process materials and components, in any size and type of container, labeled or unlabeled (excluding sealed containers of active and inactive pharmaceutical components; any finished drug product manufactured by Sun Pharmaceutical Industries, Ltd., which may be distinguished by lot numbers containing JK or GK in the initial digits; and the following finished drug products that are manufactured by Sun Pharmaceuticals, Inc., Pharmaceutics International, Inc., or Mikart, Inc.: Benzonatate Caps 100mg, 100ct; Benzonatate Caps 200mg, 100ct; Bethanechol Tabs 5mg, 100ct; Bethanechol Tabs 10mg, 100ct; Bethanechol Tabs 25mg, 100ct Bethanechol Tabs 50mg, 100ct; Gemfibrozil Tabs 600mg, 60ct; Gemfibrozil Tabs 600mg, 500ct; Hydrocodone w/APAP C-III Tabs 5 mg/325mg, 100ct; Hydrocodone w/APAP C-III Tabs 5mg/325mg, 500 ct; Hydrocodone w/APAP C-III Tabs 7.5mg/325mg, 100ct; Hydrocodone w/APAP C-III Tabs 7.5mg/325mg, 500 ct; Hydrocodone w/APAP C-III Tabs 10mg/325mg, 100 ct; Hydrocodone w/APAP C-III Tabs 10mg/325mg, 500ct; Nimodipine Caps 30mg, 30UD; Nimodipine Caps 30mg, 100UD; Oxycodone HCl C-II Tabs 5mg, 100ct; Oxycodone HCl C-II Tabs 15mg, 100ct; Oxycodone HCl C-II Tabs 30mg, 100ct; Promethazine HCl Oral Solution (Syrup)

6.25mg/5mL, 4oz; Promethazine HCl Oral Solution (Syrup) 6.25mg/5mL, 16 oz; Promethazine HCl Tabs 12.5mg, 100ct; Promethazine HCl Tabs 25mg, 100ct; Promethazine HCl Tabs 50mg, 100ct; Synalgos DC Caps 16mg/356.4mg/30mg, 100ct; Hydrocodone/APAP 100ct; and Hydrocodone/APAP 500ct), which are located anywhere on the premises of Caraco Pharmaceutical Laboratories, Ltd., 1150 Elijah McCoy Drive, Detroit, Michigan, 24700 Crestview Court, Farmington Hills, Michigan, and 31060 Oak Creek Drive, Wixom, Michigan, to which may be affixed labels bearing, among other things, the name and address of the manufacturer, packer, or distributor located outside the State of Michigan, or which are otherwise determined to consist of whole or in part of components that have originated outside the State of Michigan,

Defendants.

No.: 09-12498

CONSENT DECREE OF CONDEMNATION, FORFEITURE, AND PERMANENT INJUNCTION

On June 24, 2009, the United States of America, plaintiff, filed a Verified Complaint for Forfeiture against the articles described in the above caption.

On June 25, 2009, this Court issued a Warrant for Arrest in rem directing the United States Marshal for this district to seize the articles. The U.S. Marshal executed the seizure on June 25, 2009. Thereafter, the United States caused notice of the complaint and seizure to be published in accordance with the applicable rules of this Court.

On July 13, 2009, the United States amended its Complaint to exclude from the seizure certain products that were manufactured by third parties and only distributed by Caraco.

The articles proceeded against are articles of drug within the meaning of the Federal Food, Drug, and Cosmetic Act ("Act"), 21 U.S.C. § 321(g)(1). The amended complaint alleges that the seized articles are adulterated while held for sale after shipment of one or more of their components in interstate commerce, within the meaning of the Act, 21 U.S.C. § 351(a)(2)(B), in that the methods used in, and the facilities and controls used for, their manufacture, processing, packing, and holding do not conform to and are not operated and administered in conformity with current good manufacturing practice ("CGMP") requirements for drugs. See 21 C.F.R. Parts 210 and 211.

On July 15, 2009, Caraco Pharmaceutical Laboratories, Ltd. ("Caraco" or "Claimant") intervened and filed a claim to all of the seized articles. No other party filed a claim to the seized articles within the time allowed pursuant to Rule G of the Supplemental Rules for Admiralty or Maritime Claims and Asset Forfeiture Actions.

Claimant, having appeared and voluntarily consented to the entry of this Decree without contest, solely for the purposes of settling this case, without admitting any of the allegations of the Complaint, and before any testimony has been taken, and waiving the filing and service of an amended complaint seeking injunctive relief, and the United States having consented to this Decree:

IT IS HEREBY ORDERED, ADJUDGED, AND DECREED THAT:

1. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. § 1345 and 21 U.S.C. §§ 332 and 334, and personal jurisdiction over all parties to this action.

2. Claimant affirms that it is the sole owner of the seized articles, and it shall hold the United States harmless should any party or parties hereafter file or seek to file a claim or to intervene in this action and obtain any part of the seized articles.

3. The complaint alleges that the seized articles are adulterated while held for sale after shipment of one or more of their components in interstate commerce, within the meaning of the Act, 21 U.S.C. § 351(a)(2)(B), in that the methods used in, and the facilities and controls used for, their manufacture, processing, packing, and holding do not conform to and are not operated and administered in conformity with current good manufacturing practice (CGMP) requirements for drugs, 21 C.F.R. Part 211.

4. The seized articles are therefore condemned pursuant to 21 U.S.C. § 334(a) and forfeited to the United States.

5. Pursuant to 21 U.S.C. § 334(d), Claimant shall pay to the United States all court costs and fees, storage, and other proper expenses to date, and such additional expenses as may hereinafter be incurred and taxed. Claimant shall pay these costs in full within thirty (30) calendar days of receiving written notice from the Food and Drug Administration ("FDA") of such costs.

6. Nothing in this Decree shall prohibit Claimant

from distributing any FDA-approved drug products that are manufactured or processed, held, or distributed at or by a third party or parties, so long as Caraco did not perform any manufacturing or processing functions with respect to such drugs, and Claimant's responsibility is that of a distributor, including hydrocodone/APAP 10 mg/660 mg. (100 ct) and 10 mg./660 mg. (500 count), manufactured by Sun Pharmaceuticals Industries, Inc.; nor shall this Decree prevent Claimant from distributing, promethazine with codeine, manufactured by Sun Pharmaceuticals Industries Inc., once the product receives ANDA approval.

7. Upon notification from the United States Attorney, the United States Marshal for this District shall release the appropriate Lot of Articles (as described in subparagraphs A-C of this paragraph) from his custody to the custody of the Claimant for the sole purpose of attempting to bring the Articles into compliance with the Act, if Claimant, within twenty (20) calendar days from the date of this Decree, (a) pays in full the court costs, fees, and storage and other proper expenses of this proceeding to date as described in paragraph 5 of this Decree; and (b) executes and files with the Clerk of this Court a good and sufficient penal bond in the form of a bond or an irrevocable standby letter of credit in the amount of fifteen million dollars ($15,000,000) to be applied to Lot 1 (as described in Subpart A of this paragraph) and held for application to succeeding Lots 2-3 (as described in subparagraphs B-C of this paragraph), payable to the United States of America, and conditioned on the Claimant's abiding by and performing all of the terms and conditions of this Decree and such further orders and decrees as may be entered in this proceeding.

Said irrevocable standby letter of credit shall be obtained from a trust company or a commercial bank in good standing, shall be valid for at least ninety (90) calendar days from the date this Decree is entered, shall be approved by this Court, and may be drawn upon by the presentation of a sight draft. The schedule for release of the Articles is as follows:

A. The Articles in Lot 1, consisting of raw materials that have been opened by Claimant for the limited purpose of quality control sampling, which represent approximately one-third of the articles (by value), to be further designated by the FDA representative, shall be released to Claimant for the purpose of attempting to bring Lot 1 into compliance with the law, following payment of the costs described in Paragraph 5 and the filing of the bond or irrevocable standby letter of credit.

B. If and only if Claimant complies with all of the terms of this Decree with respect to Lot 1, and Lot 1 has been released in writing by FDA, the Articles in Lot 2, consisting of approximately a second one-third of the seized articles (by value), to be further designated by the FDA representative, shall be released to Claimant for the purpose of attempting to bring Lot 2 into compliance with the law.

C. If and only if Claimant complies with all of the terms of this Decree with respect to Lot 2, and Lot 2 has been released in writing by FDA, the Articles in Lot 3, consisting of the remaining seized Articles, shall be released to Claimant for the purpose of attempting to bring Lot 3 into compliance with the law.

D. If Claimant will not be able to complete the process of attempting to bring the Articles into com-

pliance with the law prior to the expiration of the original bond or irrevocable standby letter of credit, or any subsequent bond or irrevocable standby letter of credit, it shall be the responsibility of Claimant to file with the Clerk of this Court a new bond or irrevocable standby letter of credit in the amount of fifteen million dollars ($15,000,000), valid for at least an additional ninety (90) calendar days, no later than five (5) calendar days before the expiration of the previous bond or irrevocable standby letter of credit, and to provide written notice of the posting of such new bond or letter of credit to both FDA and the United States Attorney. If, five (5) calendar days before the expiration of the original bond or irrevocable standby letter of credit, or any subsequent bond or irrevocable standby letter of credit, Claimant has not completed the process of bringing the Articles into compliance with the law and Claimant has not filed a new bond or irrevocable standby letter of credit with the Clerk of this Court, the existing bond or irrevocable standby letter of credit shall be forfeited and immediately payable to the United States of America prior to expiration of such irrevocable standby letter of credit.

8. Claimant shall at all times, until the Articles have been released by an FDA representative, retain intact each Lot of articles seized for examination or inspection by the FDA representative, and shall maintain the records or other proof necessary to establish the identity of the Articles comprising each Lot to the satisfaction of the FDA representative.

9. After paying the costs pursuant to paragraph 5 above and filing the bond with the clerk of this court pursuant to paragraph 7 above, Claimant shall give written notice to FDA that Claimant, at its own ex-

pense, is prepared to attempt to bring the condemned articles into compliance with the law under the supervision of a duly authorized FDA representative.

10. Claimant shall not commence, permit any other person to commence, or cause any other person to commence attempting to bring the condemned articles into compliance with the law unless and until Claimant (a) submits a written statement to FDA detailing Claimant's proposed plan to bring the condemned articles into compliance with the law (the "Proposal"); (b) receives written approval of the Proposal from FDA with authorization from FDA to commence attempting to bring the condemned articles into compliance with the law. The FDA shall respond in writing to Claimant's Proposal, approving or disapproving the Proposal, within twenty (20) calendar days of receipt.

For purposes of the articles in Lot 1 only, Claimant may submit a certification from its CGMP expert that the articles in Lot 1 are in compliance with the law, in lieu of a Proposal in paragraph 10(a). Such certification shall include the bases for the certification. FDA shall approve or disapprove of such certification within fifteen (15) calendar days of receipt. If FDA approves such certification for any articles in Lot 1, FDA shall release such articles. If FDA does not approve the certification for any of the articles in Lot 1, such articles shall be subject to paragraph 10(a) and (b).

11. Within five (5) calendar days of the FDA's written approval and authorization identified in paragraph 10, the United States Attorney shall notify the United States Marshal for this District that FDA has authorized the Claimant to commence recondi-

tioning. The Marshal shall release the condemned articles from his custody to the custody of Claimant for the sole purpose of attempting to bring such articles into compliance with the law pursuant to the Proposal described in paragraph 10.

12. Claimant shall at all times, until the condemned articles have been released in writing by an FDA representative, retain the condemned articles intact for examination or inspection by the FDA representative in a place made known to and approved by FDA, and shall maintain the records or other proof necessary to establish the identity of the articles to the satisfaction of the FDA representative.

13. Within sixty (60) calendar days of receiving written authorization to commence attempting to bring the condemned articles into compliance with the law, Claimant shall complete its attempt to bring the condemned articles into compliance in accordance with the Proposal approved pursuant to paragraph 10, and under the supervision of FDA. Claimant shall destroy any article that has not been brought into compliance within ninety (90) calendar days of receiving written authority to commence implementing the Proposal, at its own expense and under the supervision of FDA, and shall file a notice with the court certifying that such articles have been destroyed.

14. Claimant shall not sell, ship, destroy, dispose of, or permit or cause another person to sell, ship, destroy, or dispose of, the condemned articles or any part of them in any manner contrary to the provisions of the Act, or other laws of the United States, or of any State or Territory (as defined in the Act), in which they are disposed of or sold. Except as provided in Paragraph 13, Claimant shall at no time, and un-

der no circumstances whatsoever, directly or indirectly, cause or permit the shipment, sale, offer for sale, or other disposal of the condemned articles until:

A. FDA has had free access to the condemned articles in order to take any samples or make any tests or examinations that are deemed necessary; and

B. FDA has released, in writing, the condemned articles for shipment, sale, or other disposition. Such a release will be granted or denied within ten (10) calendar days of Claimant's request.

15. If Claimant breaches any condition of this Decree, or any subsequent Decree or order in this proceeding, Claimant shall immediately return legal custody of any of the condemned articles that have been released by FDA pursuant to paragraph 10(b) to the United States Marshal for this District, or otherwise dispose of them at its own expense pursuant to an order of this Court. In the event that return of any of the condemned articles becomes necessary pursuant to this paragraph, Claimant shall be responsible for all costs of storage and disposition that are incurred by the United States.

16. If, within ninety (90) calendar days of the entry of this Decree, Claimant does not submit a Proposal as described in paragraph 10 above, Claimant, at its own expense and under the supervision of FDA, shall destroy such articles and make due return to this court regarding their disposition. Claimant shall reimburse the United States for any costs incurred pursuant to this paragraph, and shall pay such costs within thirty (30) calendar days of receiving an invoice from FDA.

17. The provisions in paragraphs 7-16 shall not apply to the following products:

A. Exhibit batches (also known as submission batches) that are the subject of bioequivalence testing studies for abbreviated new drug applications previously submitted or to be submitted to FDA for approval;

B. Retains;

C. Stability samples; and

D. Products that are the subject of pending or threatened litigation, which may be preserved in limited quantities for evidentiary purposes only, for so long as that need exists, but shall be destroyed under FDA supervision when that need no longer exists.

Claimant must identify any products that it intends to have covered in paragraph 17(A)-(D) to FDA and receive FDA's written approval that such products qualify for this paragraph. Claimant will isolate and hold all articles subject to this paragraph in a manner approved by FDA that ensures that any such articles in its possession, custody, and control are not introduced into interstate commerce.

18. Should Claimant fail to abide by and perform all the terms and conditions of paragraphs 5-16 above or any such further order or Decree as may be entered in this proceeding relating to attempts to bring the condemned articles into compliance with the law, through reconditioning or destruction, then the bond or irrevocable standby letter of credit described in paragraph 7 above shall, on motion of the United States in this proceeding, be forfeited in its entirety or in such part as FDA, in its discretion, determines is appropriate to the United States of America and judgment entered thereon, and any condemned articles remaining in the custody of the United States Marshal shall be forfeited and disposed of pursuant to

further order of this Court.

19. The United States Attorney for this District, upon being advised by an FDA representative that (a) all of the condemned articles have been brought into compliance with the Act and the requirements of this Decree, or destroyed in compliance with this Decree; and (b) that Claimant has paid all costs submitted to Claimant as of that date, will transmit such information to the clerk of this Court, whereupon the bond given in this proceeding shall be returned to the Claimant. The FDA shall notify the United States Attorney within five (5) business days after Claimant has completed (a) and (b).

20. Upon entry of this Decree, Claimant and each and all of its officers, directors, agents, representatives, employees, successors, assigns, attorneys, and any and all persons in active concert or participation with any of them (including individuals, directors, corporations, subsidiaries, affiliates, and partnerships) who receive actual notice of the Decree, are permanently restrained and enjoined under 21 U.S.C. § 332(a) from directly or indirectly doing or causing to be done any act that:

A. Violates 21 U.S.C. § 331(a) by introducing or delivering for introduction into interstate commerce any drug that is adulterated within the meaning of 21 U.S.C. § 351(a)(2)(B); and

B. Violates 21 U.S.C. § 331(k) by causing the adulteration of any drug within the meaning of 21 U.S.C. § 351(a)(2)(B), while such drug is held for sale after shipment of one or more of its components in interstate commerce; and

C. Violates 21 U.S.C. § 331(d) by introducing or delivering for introduction into interstate com-

merce, holding for sale after shipment into interstate commerce, manufacturing, processing, packing, labeling, holding, or distributing any new drug within the meaning of 21 U.S.C. § 321(p), unless and until:

(1) an approved new drug application or abbreviated new drug application filed pursuant to 21 U.S.C. § 355 is in effect for such drug; or

(2) an investigational new drug application filed pursuant to 21 U.S.C. § 355(i) and 21 C.F.R. Part 312 is in effect for such drug, and the use and distribution of such drug conforms strictly with the investigational new drug application.

21. Except as provided in subparagraph (K) below, upon entry of this Decree, Claimant and each and all of its officers, directors, agents, representatives, employees, successors, assigns, attorneys, and any and all persons in active concert or participation with any of them (including individuals, directors, corporations, subsidiaries, affiliates, and partnerships) who receive actual notice of the Decree, are permanently restrained and enjoined under 21 U.S.C. § 332(a) from directly or indirectly, manufacturing, processing, packing, labeling, holding, introduction, or delivery for introduction into interstate commerce at or from any of Claimant's facilities, of any drug, as defined by 21 U.S.C. § 321(g)(1), unless and until:

A. Claimant's methods, facilities, and controls used to manufacture, process, pack, label, hold, and distribute drugs are established, operated, and administered in conformity with CGMP, 21 U.S.C. § 351(a)(2)(B) and 21 C.F.R. Parts 210 and 211; and:

(1) Claimant establishes and documents management control over Quality Assurance ("QA") and Quality Control ("QC") for all of its facilities, in-

cluding but not limited to Research and Development facilities and production facilities, to ensure continuous compliance with the Act, its implementing regulations, and this Decree. Responsibility for management control over QA and QC shall be vested in an individual who shall be authorized and responsible for all QA and QC functions at all of Claimant's facilities, including ensuring the establishment, implementation, and maintenance of a comprehensive written QA and QC program ("QA/QC program") to ensure that all drug products manufactured, processed, packed, held, and distributed by Claimant at all of Claimant's facilities have the safety, identity, strength, quality, purity, and potency that they purport or are represented to possess, and are in compliance with the provisions of this Decree;

(2) Claimant establishes and follows adequate written procedures for the storage and handling of components, including written procedures for executing the production and process control functions for "charge-in" of components to a batch;

(3) Claimant maintains accurate and complete inventory records of each component and reconciles the use of each lot of such component;

(4) Claimant establishes and follows adequate written procedures for the production and process control designed to assure that the drug products have the identity, strength, quality, and purity they are represented to possess;

(5) Claimant establishes and follows adequate written procedures describing the in-process controls and tests, or examinations of uniformity of drug Products;

(6) Claimant demonstrates that its equip-

ment used in the manufacturing, processing, packing, and holding of drug products is of an appropriate design to facilitate operations for its intended use;

(7) Claimant has established adequate procedures to thoroughly investigate any unexplained discrepancies and failures of batches to meet any of their specifications;

(8) Claimant has established and followed appropriate written procedures applicable to the quality control unit; and

(9) Claimant implements a quality system that rapidly identifies problems and adverse trends to ensure that emerging product quality problems are detected and corrective and preventive actions are implemented; and

(10) Claimant has established procedures to conduct follow-up to investigations of complaints; and

(11) Claimant establishes and follows adequate development and manufacturing process design procedures to control all significant variables (including material attributes and processing parameters) affecting in-process material and final drug product specifications and quality attributes; and

B. Claimant retains, at its own expense, an independent person or persons (the "CGMP expert"), who has no personal or financial relationship (other than the consulting agreement between the parties), with Claimant or with persons in the immediate families of the officers or employees of Claimant, and who by reason of background, training, education, and experience, is qualified to inspect Claimant's drug manufacturing facilities to determine whether the

methods, facilities, and controls are operated and administered in conformity with CGMP. Claimant shall notify FDA in writing of the identity and qualifications of the CGMP expert as soon as it retains such expert; and

C. Claimant shall submit a protocol that identifies the work plan for the CGMP expert and the methodology that will be used by the CGMP expert (the "work plan") to ensure that Claimant's corrective actions are implemented and that the manufacturing, processing, packing, labeling, holding, and distribution of drugs is operated and will be continuously administered in conformity with CGMP. In addition to assuring general conformance with CGMP, the work plan must address, to FDA's satisfaction, the requirements in paragraph 21(A)(1)-(11). Within twenty (20) calendar days of receiving Claimant's work plan, FDA shall notify the Claimant in writing whether part or all of the work plan is approved. Claimant shall first obtain FDA's written approval of the work plan prior to the CGMP expert performing his or her inspection as set forth in paragraph 21(D)-(F); and

D. The CGMP expert shall perform a comprehensive inspection of Claimant's facilities and the methods and controls used to manufacture, process, package, label, hold, and distribute drugs. The CGMP expert shall determine whether Claimant's facilities and the methods and controls used to manufacture, process, package, label, hold, and distribute drugs are in compliance with CGMP; and

E. The CGMP expert shall evaluate whether Claimant has established and implemented a comprehensive written QA/QC program that is adequate

to ensure continuous compliance with the Act, its implementing regulations, and this Decree. The CGMP expert, at a minimum, shall determine whether the QA/QC program:

(1) Satisfies all requirements in paragraph 21(A);

(2) Includes written standard operating procedures ("SOPs") specifying the responsibilities and procedures applicable to QA or QC personnel and that establish mechanisms to ensure such SOPs are followed; and

(3) Establishes mechanisms to ensure that written SOPs are periodically re-evaluated so that they remain in continuous compliance with CGMP, and that the SOPs address all facets of CGMP and are reviewed and controlled by an independent QA unit; and

F. The CGMP expert certifies in writing to FDA that:

(1) He or she has inspected Claimant's facilities, methods, processes, and controls;

(2) Claimant has satisfied all requirements in paragraphs 21(A) and 21(E);

(3) All CGMP deviations brought to Claimant's attention since May 1, 2008, by FDA, the CGMP expert, or any other source, including but not limited to any experts hired prior to the entry of this Decree, have been corrected;

(4) Such facilities, methods, processes, and controls are in compliance with the requirements of CGMP; and

(5) As part of this certification, the CGMP

expert shall include a complete and detailed report of the results of his or her inspection that includes all findings of deviations from CGMP, if any; and

G. Claimant submits to FDA for approval a written batch certification protocol ("certification protocol"), and shall not commence batch certification until FDA has first approved the certification protocol in writing. Within thirty (30) calendar days of receiving Claimant's certification protocol, FDA shall either reject or issue written approval of the certification protocol. Upon approval, Claimant's CGMP expert shall certify in writing that he or she has witnessed the manufacture of three (3) consecutive batches of each drug and examined the manufacturing and control records, and the raw data associated with such records for each drug, and determined that the product meets the requirements of the certification protocol; and

H. Claimant reports to FDA in writing the actions it has taken to:

(1) Correct the CGMP deviations brought to Claimant's attention by FDA since May 1, 2008, the CGMP expert, and any other source including, but not limited to, any experts hired prior to the entry of this Decree; and

(2) Ensure that the methods used in, and the facilities and controls used for, manufacturing, processing, packing, labeling, holding, and distributing drugs are operated and will be continuously administered in conformity with CGMP.

Claimant may submit two (2) interim reports under this subparagraph 21(H), which shall include the CGMP expert certification described in subparagraph 21(F) in support of requests to begin manufacturing

and distributing a particular product(s); and

I. Within thirty-five (35) calendar days following timely receipt of Claimant's first interim report under paragraph 21(H), FDA may, in its discretion and without prior notice, commence an inspection of Claimant's facilities to determine whether the requirements of this Decree have been met, and whether Claimant's facilities are operating in conformity with CGMP, the Act, its implementing regulations, and this Decree. For any subsequent interim report or a final report (if Claimant does not submit an interim report), FDA may conduct such an inspection within forty-five (45) calendar days following receipt of such reports; and

J. FDA notifies Claimant in writing that Claimant appears to be in compliance with the requirements set forth in paragraphs 21(A)-(I), which notification shall be issued no later than forty-five (45) calendar days after conclusion of any inspection, or, if FDA does not inspect Claimant's facilities, within thirty-five (35) calendar days after receiving Claimant's report under paragraph 21(H). In no circumstance may FDA's silence be construed as a substitute for written notification.

K. Nothing in paragraph 21 shall preclude Claimant from manufacturing, processing, packing, and holding drug products for the sole purpose of conducting research and development, performing equipment qualification, performing supplier qualification, validation of drug manufacturing processes, method validation, or stability studies. Claimant shall maintain in a separate file at its facilities a written log of all lot numbers of drugs manufactured under this provision, and shall promptly make such

log available to FDA upon request. None of the drugs produced under paragraph 21(K) may be distributed. Nothing in paragraph 21 shall preclude Claimant from distributing or introducing into interstate commerce finished product manufactured, packaged and labeled by third parties.

22. After Claimant has complied with paragraphs 20-21 and has provided the notifications pursuant to paragraph 21(H), Claimant shall retain an independent person or persons (the "auditor") to conduct an audit inspection of Claimant's drug manufacturing operations. After receipt of FDA notification pursuant to Paragraph 21(J), such audit inspections shall occur no less frequently than once every six (6) months for a period of no less than one (1) year; and annually thereafter for an additional period of four (4) years. . The auditor shall be qualified by education, training, and experience to conduct such inspections, and shall be without personal or financial ties (other than a consulting agreement entered into by the parties) with any of Claimant's officers or employees or their immediate families and may, if Claimant chooses, be the same person or persons described as the CGMP expert, as set forth in paragraph 21; and

A. At the conclusion of each audit inspection, the auditor shall prepare a detailed written audit report ("audit report") analyzing whether Claimant is in compliance with the Act, its implementing regulations, and this Decree, and identifying in detail any deviations therefrom ("audit report observations"). As a part of every audit report, except the first audit report, the auditor shall assess the adequacy of corrective actions taken by Claimant to correct all previous audit report observations. The audit reports shall be delivered contemporaneously to Claimant and FDA

by courier service or overnight delivery service, no later than thirty (30) calendar days after the date the audit inspection(s) is completed. If an audit report identifies deviations from the Act, its implementing regulations, or this Decree, FDA may, in its discretion, require that the five (5) year auditing cycle be extended or begin anew. In addition, Claimant shall maintain the audit reports in separate files at its facility and shall promptly make the audit reports available to FDA upon request;

B. If an audit report contains information that indicates that the Claimant is not in compliance with CGMP, Claimant shall, within forty-five (45) calendar days of receipt of the audit report, correct those observations, unless FDA notifies Claimant that a shorter time period is necessary. If, after receiving the audit report, Claimant believes that correction of the audit report observations will take longer than forty (40) calendar days, Claimant shall, within twenty (20) business days of receipt of the audit report, submit to FDA in writing a proposed schedule for completing corrections ("correction schedule") and provide justification describing why the additional time is necessary. Before becoming effective, the correction schedule must be reviewed and approved by FDA in writing prior to implementation by Claimant. The FDA will issue a written decision, approving or disapproving the correction schedule, within ten (10) calendar days of the receipt of the corrections schedule. In no circumstance shall FDA's silence be construed as a substitute for written approval. Claimant shall complete all corrections according to the approved correction schedule. Within thirty (30) calendar days of Claimant's receipt of an audit report, unless FDA notifies Claimant that a shorter time period

is necessary, or within the time period provided in a correction schedule approved by FDA, the auditor shall review the actions taken by Claimant to correct the audit report observations. Within ten (10) business days of beginning that review, Claimant shall report in writing to FDA the auditor's review and conclusions whether each of the audit report observations has been corrected and, if not, which audit report observations remain uncorrected; and

C. In addition to the foregoing audit reports, Claimant's auditor shall, with respect to each product that has been approved by FDA for distribution following the successful completion of batch certification described in paragraph 21(G) and resumption of manufacture and distribution under paragraph 21(J), report in writing to FDA on a quarterly basis, beginning with the date of entry of this Decree, whether the succeeding batches of such product(s) meet the protocol certification requirements. If any deadline in the Paragraph falls on a week-end or holiday, the deadline is continued to the next business day that is not a holiday.

23. Representatives of FDA shall be permitted, without prior notice and as and when FDA deems necessary, to inspect Claimant's facilities and take any other measures necessary to monitor and ensure continuing compliance with the terms of this Decree. During such inspections, FDA representatives shall be permitted ready access to Claimant's facilities including, but not limited to, all buildings, equipment, finished and unfinished materials and products, containers, labeling, and other promotional material therein; to take photographs and make video recordings; to take samples of Claimant's finished and unfinished materials and products, containers, labeling,

and other promotional material; and to examine and copy all records relating to the manufacture, processing, packing, labeling, holding, and distribution of any and all of Claimant's drugs, including components thereof, in order to ensure continuing compliance with the terms of this Decree, the Act, and its implementing regulations. The inspections shall be permitted upon presentation of a copy of this Decree and appropriate credentials. The inspection authority granted by this Decree is separate from, and in addition to, the authority to make inspections under the Act, 21 U.S.C. § 374.

24. If, at any time after entry of this Decree, FDA determines, based on the results of an inspection, the analysis of a sample, a report or data prepared or submitted by Claimant, the CGMP expert, the auditor, or any other information, that Claimant has failed to comply with any provision of this Decree, has violated the Act or its implementing regulations, or that additional corrective actions are necessary to achieve compliance with this Decree, the Act, or its implementing regulations, FDA may, as and when it deems necessary, order Claimant in writing to take appropriate corrective actions, including, but not limited to, the following:

A. Cease all manufacturing, processing, packing, repacking, labeling, holding, and/or distributing any or all drug(s);

B. Recall, at Claimant's expense, any drug manufactured, processed, packaged, labeled, held, or distributed by Claimant that is adulterated, misbranded, or otherwise in violation of this Decree, the Act, or its implementing regulations;

C. Revise, modify, or expand any report(s) or

plan(s) prepared pursuant to this Decree;

D. Submit additional reports or information to FDA;

E. Issue a safety alert with respect to a drug manufactured, processed, packaged, labeled, held, or distributed by Claimant; and/or

F. Take any other corrective actions with respect to any drug manufactured, processed, packaged, labeled, held, or distributed by Claimant as FDA in its discretion, deems necessary to bring Claimant into compliance with this Decree, the Act, or its implementing regulations.

25. Unless a different time frame is specified by FDA in its order under paragraph 24, within five (5) business days after receiving an order pursuant to paragraph 24, Claimant shall notify FDA in writing either that (1) the Claimant is undertaking or has undertaken corrective action, in which event Claimant shall also describe the specific action taken or to be taken and the schedule for completing the action; or (2) the Claimant does not agree with FDA's order. If the Claimant notifies FDA that it does not agree with FDA's order, the Claimant shall explain in writing the basis for the disagreement; in so doing, the Claimant may also propose specific alternative actions and specific time frames for achieving FDA's objectives.

26. If the Claimant notifies FDA in writing that it does not agree with FDA's order, FDA will review the Claimant's notification and thereafter, in writing, affirm, modify, or withdraw its order, as FDA deems appropriate.

27. If FDA affirms or modifies its order, the Clai-

mant shall, upon receipt of FDA's order, immediately implement the order (as modified, if applicable) and, if the Claimant so chooses, bring the matter before this Court on an expedited basis. All decisions specified in this Decree shall be vested in FDA's discretion and, if necessary, shall be reviewed by this Court pursuant to the terms set forth in paragraph 34 of this Decree.

28. The process and procedures set forth in paragraphs 25-27 shall not apply to any order issued pursuant to paragraph 24 if such order states that, in FDA's judgment, the matter raises significant public health concerns. In such case, Claimant shall immediately and fully comply with the terms of that order. Should Claimant seek to challenge any such order, it may petition this Court for relief.

29. Any cessation of operations or other action described in paragraph 24-28 shall continue until Claimant receives written notification from FDA that Claimant appears to be in compliance with this Decree, the Act, and its implementing regulations, and that Claimant may, therefore, resume operations. Upon Claimant's written request to resume operations, FDA shall determine within a reasonable time of receipt of the request whether Claimant appears to be in such compliance, and, if so, issue to Claimant a written notification permitting resumption of operations. The costs of FDA supervision, inspections, investigations, analyses, examinations, reviews, sampling, testing, travel time, and subsistence expenses to implement the remedies set forth in this paragraph and paragraph 24, shall be borne by Claimant at the rates specified in paragraph 31 of this Decree.

30. The parties may at any time petition each

other in writing to extend any deadline provided for herein; and, if the parties mutually agree to extend a deadline, such extension may be granted without seeking leave of Court.

31. Claimant shall reimburse FDA for the costs of all FDA inspections, investigations, supervision, reviews, examinations, and analyses that FDA deems necessary to evaluate compliance with this Decree. The costs of such inspections shall be borne by Claimant at the prevailing rates in effect at the time the costs are incurred. As of the date that this Decree is signed by the parties, these rates are: $85.49 per hour and fraction thereof per representative for inspection work; $102.49 per hour or fraction thereof per representative for analytical or review work; $0.55 per mile for travel expenses by automobile; government rate or the equivalent for travel by air or other means; and the published government per diem rate or the equivalent for the areas in which the inspections are performed per-day, per-representative for subsistence expenses, where necessary. In the event that the standard rates applicable to FDA supervision of court-ordered compliance are modified, these rates shall be increased or decreased without further order of the Court.

32. Within fifteen (15) business days after the date of entry of this Decree, Claimant must provide a list to FDA of all drugs that it has manufactured or distributed within one year before the date of entry of this Decree, or that it intends to manufacture or distribute within one year following the date of entry of this Decree, that do not have an approved new drug application or an approved abbreviated new drug application filed pursuant to 21 U.S.C. § 355.

33. The provision in paragraph 20(C) shall not apply to Choline Magnesium Trisalicylate. Within two (2) months of the date of entry of this decree, Claimant shall provide to FDA details of a plan for submitting an application for approval of Choline Magnesium Trisalicylate, or for establishing an exemption for that drug. Such plan shall not be implemented until approved in writing by FDA. If Claimant does not provide FDA with a plan for submitting an application for approval of, or a plan that establishes an exemption for, Choline Magnesium Trisalicylate that is acceptable to FDA within six (6) months after the date of entry of this decree, then FDA may, in its discretion, apply paragraph 20(C) to Choline Magnesium Trisalicylate.

34. Claimant shall abide by the decisions of FDA and its representatives, which shall be final. All decisions specified in this Decree shall be vested in FDA's discretion and, if necessary, shall be reviewed by this court pursuant to the arbitrary and capricious standard as set forth in 5 U.S.C. § 706(2)(A).

Review by a court of any FDA decision rendered pursuant to this Decree shall be conducted without any discovery and shall be based exclusively upon the written record that was before FDA at the time of the decision.

35. Should the United States bring, and prevail in, a contempt action to enforce the terms of this Decree, Claimant shall, in addition to other remedies, reimburse the United States for its attorneys' fees, investigational expenses, expert witness fees, travel expenses incurred by attorneys and witnesses, and administrative court costs relating to such contempt proceedings.

36. Claimant shall notify FDA, at the address specified in paragraph 39 below, at least ten (10) business days before any of the following events occur or within ten (10) calendar days after learning that any of the following events will occur if the event would affect Claimant's compliance obligations arising out of this Decree: any reorganization, relocation, dissolution, assignment, or sale resulting in the emergence of a successor corporation, the creation of dissolution of subsidiaries, or any other change in its legal status.

37. Within ten (10) business days of the date of entry of this Decree, Claimant shall provide a copy of the Decree, by personal service, personal delivery via electronic mail with acknowledgment of receipt, return receipt email, or certified mail (restricted delivery, return receipt requested), to each and all of the following "Associated Persons": employees, directors, officers, agents, representatives, attorneys, successors, and assigns of Claimant, and any and all persons or entities in active concert or participation with any of them, including, but not limited to, all others involved in the manufacture of Claimant's products. In the event that Claimant becomes associated, at any time after the entry of this Decree, with new Associated Persons, Claimant shall within fifteen (15) calendar days of such association provide a copy of this Decree to such person(s) by electronic mail with acknowledgment of receipt, return receipt email, or certified mail (restricted delivery, return receipt requested). Within twenty (20) calendar days of the date of entry of this Decree, Claimant shall hold a general meeting or a series of smaller meetings for all persons with responsibility for operations and manufacturing at any facility where Claimant holds ar-

ticles of drug for introduction into interstate commerce, and upon the opening of any new such facility, at which it shall describe the terms and obligations of this Decree. Within thirty (30) calendar days of the date of entry of this Decree, Claimant shall furnish FDA with an affidavit of compliance with this paragraph (signed by a person with personal knowledge of the facts). Such affidavit should identify the names, addresses, and positions of all new Associated Persons that received a copy of the Decree.

38. Claimant shall post a copy of this Decree on a bulletin board in the employee common area of any distribution facility where Claimant holds articles of drug for introduction into interstate commerce, within ten (10) calendar days of the entry of this Decree or, if any new such facility is opened, within ten (10) calendar days of opening, and shall ensure that the Decree remains posted for a period of at least one year. Within thirty (30) calendar days of the date of entry of this Decree, Claimant shall provide to FDA an affidavit (signed by a person with personal knowledge of the facts) stating the fact and manner of its compliance with this paragraph.

39. All notifications, correspondence, and communications to FDA required by the terms of this Decree shall be marked "Consent Decree Correspondence" and shall be addressed to: District Director, FDA Detroit District Office, 300 River Place, Suite 5900, Detroit, MI, 48207.

40. If Claimant fails to comply with any of the provisions of this Decree, including any time frame imposed by this Decree, then, on motion of the United States in this proceeding, Claimant shall pay to the United States of America: ten thousand dollars ($10,000) in liquidated damages for each day such vi-

olation continues; an additional sum of ten thousand dollars ($10,000) in liquidated damages for each violation of the Act, its implementing regulations, and/or this Decree; and an additional sum equal to twice the retail value of each shipment of an adulterated drug, in liquidated damages for each such unlawful shipment. Any penalty imposed under this paragraph shall not exceed five million dollars ($5,000,000) in any calendar year. The remedy in this paragraph shall be in addition to any other remedies available to the United States under this Decree or the law.

41. This Court retains jurisdiction to issue such further decrees and orders as may be necessary to the proper disposition of this proceeding.

ENTER

/s/ Arthur J Tarnow
United States District Judge

Dated this 29th day of September, 2009

Entry consented to:

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UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants.

Civil Action No.: 4:05 CV 40188
Hon. Avern Cohn

STIPULATION REGARDING CLAIM 5 OF '358 PATENT

WHEREAS, the parties desire to streamline the pending ANDA litigation; and,

WHEREAS, Novo Nordisk is presently asserting claims 4 and 5 of the '358 patent in said litigation;

The parties hereby STIPULATE and AGREE as follows:

A. Novo Nordisk agrees not to pursue any claim for infringement by Caraco of claim 5 of the '358 patent in the pending ANDA litigation. This agreement shall remain in effect provided there are no future substantive amendments to Caraco's ANDA bearing on claim 5;

B. Caraco agrees not to pursue any claim for invalidity of claim 5 of the '358 patent in the captioned ANDA litigation;

C. Notwithstanding the foregoing, Caraco is maintaining its Paragraph IV certification with the FDA as to claims 1-3 and 5 of the '358 patent in its pending ANDA, and nothing in this stipulation shall be deemed to affect said certification;

D. Neither Novo Nordisk nor Caraco are waiving, or in any way compromising, any right to pursue any claim of infringement or invalidity, respectively, outside of the context of the pending ANDA litigation; and,

E. Before the commencement of trial, Caraco shall withdraw any evidence relating solely to claim 5.

* * * *

[Signature Blocks and Certificate of Service Omitted]

Dated: October 2, 2009

No. 2010-1001

IN THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Appellants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Appellees.

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE EASTERN DISTRICT OF MICHIGAN CASE NO. 2:05-CV-40188, JUDGE AVERN COHN

OPPOSITION TO PLAINTIFFS-APPELLANTS' EMERGENCY MOTION TO STAY MANDATORY INJUNCTION PENDING APPEAL

* * * *

[Signatures, Certificate of Interest,Table of Contents, Table of Authorities, Index of Abbreviations, Index of Exhibits, and Confidentiality Statement Omitted]

INTRODUCTION AND SUMMARY OF ARGUMENT

The Court should deny Novo Nordisk's "emergency" motion to stay the mandatory injunction entered below. That injunction requires Novo to tell FDA what the patent-in-suit actually covers—nothing more. Novo seeks to block this "truth-telling"

injunction so it can continue to mischaracterize its patent to delay legitimate generic competition. As the District Court put it, Novo's arguments are "a farrago of misstated and irrelevant facts and misstated law." Ex. 1 at 2.

This case concerns repaglinide, a diabetes drug sold by Novo as "Prandin." FDA has approved the drug for three separate uses: repaglinide by itself, repaglinide in combination with a class of antidiabetic drugs known as TZDs, and repaglinide in combination with another antidiabetic drug called metformin. Novo held a patent on repaglinide, but that patent has expired.

Caraco has filed an ANDA to sell generic repaglinide. Novo sued Caraco and alleges that such a generic launch would infringe its sole remaining repaglinide patent (the '358 patent). This patent covers only the third FDA-approved use of the drug, i.e., the use of "repaglinide in combination with metformin." Ex. 3. But Caraco has no plans to market its repaglinide ANDA product at issue for this patented use. It therefore asked FDA for permission to omit—or "carve out"—all references to this combination therapy from its generic label. FDA approves such a carve-out only if the remaining uses on the label are not claimed by a patent.

FDA, however, does not construe patents. Instead, it requires NDA holders to identify all method patents covering a referenced drug and, for each such patent, to describe accurately and succinctly the approved use claimed by that patent. FDA refers to this patent characterization as a "use code description." When evaluating a proposed labeling carve-out, FDA performs the ministerial task

of comparing the proposed label to the NDA holder's use code description to ensure that the generic label will not support a claim for patent infringement.

From 1997 to May 2009, Novo's use code description accurately characterized the '358 patent as covering the "use of repaglinide in combination with metformin to lower blood glucose." Ex. 15 at 3. Based on this patent description, FDA ruled in December 2008 that Caraco could properly omit the patented use from its label. Ex. 7. This ruling allowed Caraco to market a non-infringing repaglinide product, thus paving the way for generic competition.

To delay such competition, Novo changed its use code description in May to read: "a method for improving glycemic control in adults with type 2 diabetes mellitus." Ex. 8 at 3. FDA cannot tell from this vague patent description which of the three approved methods of using repaglinide is covered by the '358 patent. And Novo refuses to tell FDA what method its patent really covers. FDA thus cannot determine whether Caraco's generic label does indeed excise the patented use while leaving intact the unpatented ones. As a result, FDA has reversed itself and rejected Caraco's proposed labeling carve out—forcing Caraco to include the patented metformin-repaglinide combination therapy in its label. Such a label could induce infringement of the '358 patent and allow Novo to prevent Caraco from launching until the patent expires in 2018.

The District Court properly entered a mandatory injunction under the Hatch-Waxman Act that requires Novo to restore its original, and proper, use code description for the '358 patent. Novo asks to

stay that injunction so it can continue to mislead FDA. But Novo has failed to meet its burden to justify such a stay.

First, Novo cannot show a likelihood of success on the merits. The Hatch-Waxman counterclaim provision authorized the District Court to enter its injunction "to correct . . . patent information submitted by [Novo] under" Food, Drug, and Cosmetic Act (FDCA) Sections 355 (b) and (c). 21 U.S.C. § 355 (j)(5)(C)(ii)(I). Novo argues that it did not submit its new use code description "under" these provisions. But this ignores the plain language of the statute and Novo's own submission. The form on which Novo tendered its new patent description confirms that it was "submitted under FDCA § 355 (b) and (c)."

The District Court's injunction is warranted here because Novo's amended use code description "seriously misrepresents the approved method of use covered by" the '358 patent. Ex. 1 at 4. That is, Novo's new patent description is "so broad as to incorrectly suggest that the '358 patent generically covers three (3) different FDA-approved methods of use of repaglinide," despite Novo's admission that "the first two (2) uses are not covered by claim 4 of the '358 patent." *Id.* at 2.

Second, Novo will not be irreparably harmed if it were required to tell FDA what its patent actually covers. Novo says it needs a stay because telling FDA the truth would allow Caraco to launch a generic product that does not include information on the patented method of use. By definition, such a launch would *not* infringe Novo's patent. So Novo would not be harmed at all.

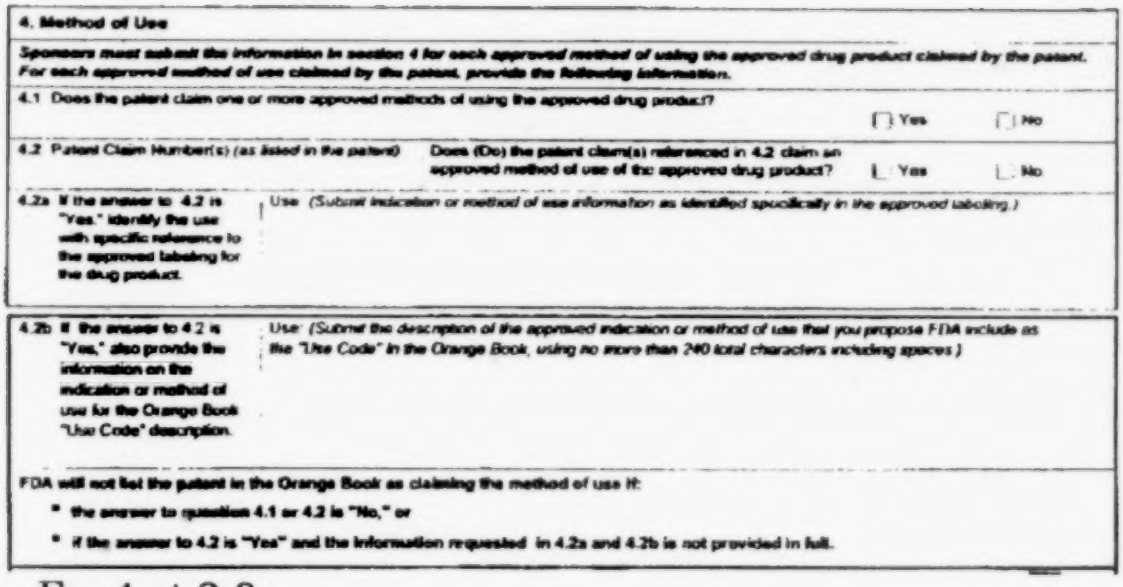
Third, the balance of hardships and public interest factors favor Caraco. A stay would reward Novo's fraudulent effort to block legitimate generic competition and encourage similar mischief. Denying the stay, in contrast, would help facilitate the launch of a less expensive generic diabetes drug.

In the end, there is no basis to stay an injunction that merely requires Novo to tell FDA what the '358 patent actually claims. And there certainly is no basis to stay trial in this case, a request Novo never made to the court below.

REGULATORY FRAMEWORK

The "Hatch-Waxman Act" refers to amendments to the FDCA that allow generic firms to obtain FDA marketing approval of their drugs by filing an Abbreviated New Drug Application (ANDA). An ANDA relies on the safety and efficacy data in a brand-name drug company's New Drug Application (NDA). To facilitate the ANDA approval process, FDCA §§ 505(b) and (c) require NDA holders like Novo to disclose and characterize any applicable patent rights. 21 U.S.C. § 355(b)(1)(G). This "patent information" is submitted by the NDA holder on Form FDA 3542 and published in a compendium known as the Orange Book. 21 U.S.C. § 355(j)(7)(A)(iii); 21 C.F.R. § 314.53.

For method patents, the NDA holder must provide, among other things, "[t]he description of the patented method of use as required for publication." 21 C.F.R. § 314.53(c)(2)(ii)(P). NDA holders create this "use code description" by completing Box 4.2b of Form FDA 3542:



4. Method of Use

Sponsors must submit the information in section 4 for each approved method of using the approved drug product claimed by the patent. For each approved method of use claimed by the patent, provide the following information.

4.1 Does the patent claim one or more approved methods of using the approved drug product? ☐ Yes ☐ No

4.2 Patent Claim Number(s) *(as listed in the patent)* — Does (Do) the patent claim(s) referenced in 4.2 claim an approved method of use of the approved drug product? ☐ Yes ☐ No

4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the approved labeling for the drug product. — Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

4.2b If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description. — Use: *(Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)*

FDA will not list the patent in the Orange Book as claiming the method of use if:

- the answer to question 4.1 or 4.2 is "No," or
- if the answer to 4.2 is "Yes" and the information requested in 4.2a and 4.2b is not provided in full.

Ex. 4 at 2-3

Novo argues that Box 4 authorizes a "use code description" that does not accurately describe the referenced method patent. This is plainly wrong. The general Box 4 instruction, when read with the instruction in Box 4.2b, unambiguously requires a description of what is "claimed by the patent":

> *For each approved method of use claimed by the patent*, provide the following information: . . . Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.

Id. (emphasis added). This interpretation comports with both the regulations and FDA's instructions on the last page of Form 3542:

> *The use code designates a method of use patent that claims the approved indication or use of a*

> *drug product. Each approved use claimed by the patent should be separately identified in this section* and contain adequate information to assist... ANDA applicants in determining whether a listed method of use patent claims a use for which the . . . ANDA applicant is not seeking approval.

Id. at 4; *see also* 68 Fed. Reg. 36676, 36682-83 (June 18, 2003) (Form 3542 "includes the complete description of the method-of-use claim and the corresponding language in the labeling of the approved drug").

Novo also ignores that use code descriptions play a critical role in the Hatch-Waxman statutory scheme. To obtain approval of an ANDA, a generic drug maker ordinarily must certify in its application that it will not infringe any valid patent listed in the Orange Book for the branded drug. *See* 21 U.S.C. § 355(j)(2)(A)(vii). For example, the generic applicant can certify that the listed patent is not infringed or invalid—known as a "Paragraph IV" certification. *See Purepac Pharm. Co.* v. *Thompson*, 354 F.3d 877, 879-880 (D.C. Cir. 2004). But where, as here, the drug itself is not patented and the generic applicant does not seek approval for a patented method of using that drug, the applicant can avoid certification by making a "section viii statement." *Id.* at 880. With a section viii statement, the generic applicant asserts that the listed method patent does not cover the uses for which it seeks approval because it will "carve out" all references to the patented method of use in the generic label. 21 U.S.C. § 355(j)(2)(A)(viii).

FDA is obligated to accept or reject Paragraph IV and section viii statements based on their compliance

with the FDCA. But it does not construe patent language. Instead, FDA accepts as true use code *patent* descriptions provided by the NDA holder to determine the scope of method patents listed in the Orange Book. 21 C.F.R. § 314.53(f); *see also* 68 Fed. Reg. 36676, 36682 ("To effectively implement the certification and section viii statement provisions set out in the statute, [FDA] must have adequate information concerning method-of-use patents" from NDA holders). To prevent abuse of the use code process, FDA requires "accurate and detailed" descriptions of method patents from the NDA holder, and requires Form 3542 to be submitted under penalty of perjury. Ex. 8 at 3; *see also Purepac Pharm. Co.* v. *Thompson*, 238 F. Supp. 2d 191, 198 (D.D.C. 2002), *aff'd*, 354 F.3d 877 (D.C. Cir. 2004) (use code descriptions are required "to determine the particular medical uses of brand-name drugs asserted by the various use patents listed in the Orange Book"). If use code descriptions do not accurately describe the Orange Book-listed method patents, the entire system breaks down. That is what happened here, and what the District Court rightly corrected.

FACTUAL BACKGROUND

FDA has approved Prandin for three uses: (1) by itself, (2) in combination with thiazolidinediones (TZDs), and (3) in combination with metformin. Claim 4 of the '358 patent covers only the third use—*i.e.*, the "method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment *repaglinide in combination with metformin*." Ex. 3 (emphasis added). Caraco filed an ANDA for repaglinide and initially included a Paragraph IV certification as to

claim 4. FDA tentatively approved Caraco's ANDA based on that certification in August 2007. Ex. 5.

But Caraco has no desire to market repaglinide under this ANDA for the patented use. Thus, in April 2008, at FDA's suggestion, Caraco applied to submit a section viii statement for claim 4. Ex. 6 at 3, 5, 11.[1] Caraco's proposed label omits all references to this patented method and thus would not infringe the '358 patent. *Warner-Lambert Co.* v. *Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003).

Novo challenged Caraco's proposed carve-out as improper and unsafe in a Citizen Petition to FDA. In December 2008, FDA held that Caraco's section viii statement was proper based on Novo's original use code description: "use of repaglinide in combination with metformin." Ex. 7 at 9-10; *see also* Ex. 9. FDA also rejected Novo's purported safety concerns. Ex. 7 at 12-14.

In May 2009, Novo amended its Orange Book use code description for Prandin to read: "A method for improving glycemic control in adults with type 2 diabetes mellitus." Ex. 8. Because FDA cannot now determine which approved use of repaglinide Novo contends the '358 patent covers, the Agency has rejected Caraco's proposed label carve-out and section viii statement. Exs. 9, 10. This rejection forces Caraco to market repaglinide for a use claimed by the '358 patent.

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[1] The record sometimes refers to a "split-certification." This is because Caraco filed a Paragraph IV certification as to claims 1-3 and 5 of the '358 patent, and a section viii statement as to method claim 4.

Caraco sought an injunction under the Hatch-Waxman counterclaim provision to restore the original and accurate use code description. On September 25, the District Court entered the requested injunction but stayed its effect for 20 days (until October 15) at Novo's request. Ex. 11. Novo filed its "emergency" motion a week later. Because Novo's misconduct has revived its infringement claim, the parties are proceeding to trial on Caraco's defenses and counterclaims of patent invalidity and unenforceability on October 14, 2009.

ARGUMENT

Novo cannot satisfy its admitted burden of showing likelihood of success on the merits, irreparable harm, *and* that the balance of hardships and public interest favor its cause. Mot. at 5-6.

I. Novo Cannot Show Likelihood Of Success On The Merits

The Hatch-Waxman Act authorizes a counterclaim "to correct ... patent information submitted by the holder under subsection (b) or (c) [of FDCA § 505] ... on the ground that the ['358] patent does not claim ... an approved method of using the drug." 21 U.S.C. § 355(j)(5)(C)(ii)(I)(bb). The District Court properly invoked this statute to enter the underlying injunction.

A. "Patent Information Submitted By The Holder Under" FDCA §§ 505(b) and (c) Includes Use Code Descriptions.

Novo primarily argues that the Hatch-Waxman counterclaim provision is limited to correcting patent numbers and expiration dates, not use code

descriptions. Novo is wrong for three separate reasons.

First, the statutory language does not support Novo's position. The counterclaim provision authorizes, in relevant part, an injunction to correct "patent information submitted by the holder under [FDCA §§ 505] (b) or (c)." Novo tries to limit the reach of this provision to correcting patent numbers and expiration dates because those are the only types of "patent information" specifically mentioned in FDCA §§ 505(b) and (c). But Novo's interpretation of the counterclaim provision would replace the phrase "patent information submitted by the holder under subsection (b) or (c)" with "patent information *described in* subsection (b) or (c)." Had Congress intended such a result, it could have used that language, which appears elsewhere in the statute. *See, e.g.*, 21 U.S.C. § 355 (c)(2) ("If the patent information *described in* subsection (b) of this section ..."). It also could have directly said that a counterclaim could be brought only to correct "the patent number or the expiration date." Congress did neither of these things.

Instead, it used the phrase "submitted by the holder." This phrase must be enforced according to its plain language. *Lamie* v. *United States Trustee*, 540 U.S. 526, 534 (2004). And it can only mean information submitted by the NDA holder to FDA under the FDCA regulations. NDA holders do not submit anything under the FDCA itself; rather, they submit patent information on Form 3542 pursuant to regulations entitled "Submission of Patent Information." 21 C.F.R. § 314.53; *see also* 68 Fed. Reg. 36676, 36697-98 (June 18, 2003) (citing Sections 505 (b) and (c) as legal authority for the regulation).

Novo's own Form 3542 submission confirms that its patent information "is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act." Ex. 8 at 2.

Importantly, Form 3542 and the related regulatory guidance discussed above all were published in the Federal Register on June 18, 2003—almost six months *before* the December 8, 2003, effective date of the Hatch-Waxman counterclaim provision. *See* Pub. L. No. 108-173, 117 Stat. 2066. "It is always appropriate to assume that our elected representatives, like other citizens, know the law." *Traynor* v. *Turnage*, 485 U.S. 535, 546 (1988). Thus, Congress is assumed to have referred to FDA's "Submission of Patent Information" regulations when it used the phrase "patent information submitted by the holder under subsection (b) or (c)."

Second, Novo's crabbed interpretation of FDCA §§ 505 (b) and (c) conflicts with FDA's own construction of those provisions, which is entitled to substantial deference. Novo argues that the statute only requires NDA holders to submit patent numbers and expiration dates. But the relevant provision of the statute requires NDA holders to identify "any patent ... which claims a method of using [the referenced] drug *and with respect to which a claim of patent infringement could reasonably be asserted*." 21 U.S.C. § 355 (b)(1) (emphasis added). Congress did not inform FDA how to determine whether a method patent could reasonably support a claim of patent infringement. FDA thus properly filled this "gap" by requiring NDA holders to describe their method patents in the use code description. *United States* v. *Mead*, 533 U.S. 218, 227 (2001); *see also* 68 Fed. Reg. 36676, 36683 (June 18, 2003). "FDA interpretations

of the FDCA receive deference." *Purepac*, 354 F.3d at 883. Yet Novo makes no effort to explain why FDA's interpretation of FDCA §§ 505 (b) and (c) is arbitrary or capricious.

Finally, as the District Court noted, Novo's reading of the counterclaim provision conflicts with the legislative history. Congress added the counterclaim provision in 2003 to create a broad private right of action designed to prevent Orange Book abuse. As Senator Charles Schumer put it: "The [new] provisions *close loopholes in the law and end the abusive practices in the pharmaceutical industry which have kept lower-priced generics off the market* and cost consumers billions of dollars." 149 Cong. Rec. 31200 (Nov. 24, 2003) (emphasis added). He went on to explain that the new counterclaim provision would cover FDA's patent listing requirements, without limitation: *"[T]he provisions enforce the patent listing requirements at the FDA* by allowing a generic applicant, when it has been sued for patent infringement, to file a counterclaim to have the brand drug company delist the patent *or correct the patent information in FDA's Orange Book*." *Id.* (emphasis added); *see also* Ex. 2 at 9-18. There is no plausible rationale for narrowly reading the counterclaim provision to allow Novo's abuse.

B. Caraco's Counterclaim Alleges That The '358 Patent "Does Not Claim An Approved Method Of Using The Drug"

Novo also argues that Caraco failed to allege that the '358 patent "does not claim ... an approved method of using the drug," as required by the Hatch-Waxman counterclaim provision. Novo relies on the fact that the '358 patent *does* claim an approved

method of use. But this argument is a logical fallacy. It conveniently ignores that repaglinide has three distinct FDA-approved methods of use. While the '358 patent may claim one of these methods, *it does not claim the other two.*

The District Court properly invoked the Hatch-Waxman counterclaim provision because Novo's use code description fails to state which of the three approved methods of use the '358 patent claims. Only by identifying with particularity what use the '358 patent does claim can FDA determine which approved methods of using repaglinide the patent "does not claim."

C. Novo's Use Code Description Must Track The '358 Patent

Novo next argues that its use code description need not accurately describe the '358 patent. This argument is frivolous. As discussed above, the regulations, FDA Final Rules and Form 3542 itself all unambiguously require use code descriptions to characterize the approved use "claimed by the patent." Ex. 4, Box 4. The District Court thus properly found that "FDA's Form 3542 requires that a Use Code narrative accurately describe each approved method of use *claimed* by a patent listed in the Orange Book. The narrative is limited to those approved uses of the drug product that the patent claims." Ex. 2 at 17 (emphasis in original).

FDA correspondence to Novo confirms this interpretation: "FDA relies on the [patentees] to craft an accurate and complete description of the relevant patent claims (to form the basis of the use code) and to identify the approved labeling that corresponds to those claims." Ex. 9. Novo understands this. It

admits that it amended its use code description [to cause FDA "to prevent generic applicants" from carving-out the patented method from their label.] Ex. 12 at ¶ 16.

D. Novo Makes No Effort To Address Caraco's Alternative Basis For The Injunction.

Novo's motion completely ignores that Caraco has alleged an alternative basis to support the injunction—patent misuse. Ex. 2 at 7-8, 18-20. The Court could affirm the injunction on this theory, which is amply supported by the District Court's decisions. *See id.* To show likelihood of reversing the injunction, Novo must defeat this alternative theory as well. *Lion Raisins, Inc.* v. *United States*, 416 F.3d 1356, 1368 (Fed. Cir. 2005) (decision can be affirmed on any ground shown by the record, whether or not the basis of the district court's decision). Yet, Novo has failed even to address Caraco's alternative allegation of patent misuse. The motion to stay should be denied for this reason alone.

II. Novo Cannot Show Irreparable Harm Absent The Stay

Novo also has failed to show irreparable harm. Novo openly asserted in a declaration that it ["has consistently told the FDA that claim 4 of the '358 patent only claims the use of repaglinide in combination therapy with metformin."] Ex. 12 at ¶ 12. The injunction merely requires Novo to say this to FDA in the use code description. Doing so could not possibly cause Novo irreparable harm.

First, Novo argues that the injunction "endangers the integrity and accuracy of Novo's NDA for PRANDIN®" because it purportedly requires Novo to characterize the '358 patent "in direct contravention

of FDA regulations." Mot. at 10. Novo has it backwards. As discussed above, the regulations require Novo to provide "[t]he description of the patented method of use as required for publication" to ensure the Hatch-Waxman process works properly. 21 C.F.R. § 314.53(c)(2)(ii)(P). Novo cites no "FDA regulation" to supports this "harm."

Second, Novo argues that it would be irreparably harmed by a generic launch *solely* for non-infringing uses—*i.e.*, a launch by Caraco with the carved-out label. But sales of generic repaglinide using such a label cannot infringe. *See Warner-Lambert*, 316 F.3d at 1354-62. This, of course, is precisely why Caraco sought approval for the section viii carve-out in the first place. Even putting aside this fatal flaw in Novo's alleged harm, its "generalized statements with no specific support" cannot suffice to show irreparable harm. *Magnesystems* v. *Nikken, Inc.*, 36 F.3d 1114, 1115 (Fed. Cir. 1994).

Novo also ignores that the requested stay itself cannot stop Caraco's launch. As Novo concedes, the 30-month stay of FDA approval has expired. Mot. at 12. So even if this Court were to enter the stay, it would not prevent FDA from approving an "at risk" launch by Caraco of generic repaglinide that includes the patented method in its label—as FDA is now requiring due to Novo's misconduct. Thus, Novo cannot argue that it needs a stay to prevent a generic launch. It can only argue that it wants a stay to continue to mislead FDA into rejecting Caraco's request to launch solely for non-infringing uses.

Finally, and most remarkably, Novo asserts that the First Amendment allows it to ignore express FDA instructions. This argument was never raised below

and thus has not been preserved. Regardless, it is ludicrous. Novo cannot invoke the First Amendment to justify misleading statements to FDA. *Cf.* 18 U.S.C. § 1001.

III. The Other "Stay" Factors Also Strongly Favor Caraco

Novo's "emergency" motion also should be denied because a stay, if granted, would allow Novo to continue to frustrate Caraco's ability to launch its generic product for non-infringing uses. Novo argues that a stay would not harm Caraco because it could take months for FDA to approve Caraco's ANDA. Thus, according to Novo, "Caraco cannot launch its product in any event." Mot. at 12. But this argument proves too much. Accepting Novo's position at face value, it has shown no need for a stay to preserve the status quo.

The reality is that FDA could approve Caraco's launch in the near future. Once that happens, every day the injunction is stayed would unduly delay Caraco's launch of a non-infringing generic product. The requested stay thus clearly would violate public policy. Indeed, it would frustrate the entire purpose of the Hatch-Waxman Act: "Congress sought to get generic drugs into the hands of patients at reasonable prices—fast." *In re Barr Labs., Inc.*, 930 F.2d 72, 76 (D.C. Cir. 1991).

Novo also argues that Caraco's proposed carved-out label would cause safety concerns. But FDA carefully considered *and rejected* this precise argument. Ex. 7 at 12-14. As the District Court aptly put it: "Novo is not a private FDA. Novo, by the change in the use code narrative is attempting to

extend the life of [its] expired [repaglinide] patent." Ex. 1 at 5.

IV. There Is No Basis To Stay The October 14 Trial

In a last-ditch effort, Novo asks this Court on interlocutory appeal to take the extraordinary step of staying a trial on completely unrelated issues—in an infringement action *Novo* filed in 2005. According to Novo, the District Court somehow divested itself of Hatch-Waxman jurisdiction when it entered the injunction at issue here. Once again, Novo is wrong.

First, Novo never raised this argument before the District Court, which is best equipped to address jurisdictional issues affecting a trial in the first instance. *See, e.g.*, *United States* v. *Ziegler Bolt & Parts Co.*, 111 F.3d 878, 883 (Fed. Cir. 1997) ("On appeal, this court defers to the judgment of the trial court on such matters closely associated with the standard functions of the adjudicative process, so long as that judgment is not an abuse of the trial court's discretion").

Second, the District Court's Hatch-Waxman jurisdiction is fully intact. As Novo admits, FDA has rejected Caraco's section viii statement, thus requiring Caraco to maintain its original Paragraph IV certification against claim 4. Mot. at 4. At a bare minimum, the District Court retains Hatch-Waxman jurisdiction over the case unless and until FDA actually approves Caraco's application to convert from the Paragraph IV certification to a section viii statement. And Novo's motion to stay is designed for the precise purpose of preventing that from happening.

Third, the trial can go forward even if the District Court lacks jurisdiction under the Hatch-Waxman Act (which it does not). This is because Novo's infringement claim is based not only under the Hatch-Waxman Act, but also under 35 U.S.C. § 271(b); Ex. 13 at ¶ 22. Additionally, the District Court has jurisdiction under the Declaratory Judgment Act, 28 U.S.C. § 2201, to try Caraco's counterclaims for declaratory judgments of invalidity and unenforceability. Ex. 14 at ¶¶ 30-33,96-101. There most certainly is an actual controversy as to whether an imminent launch of generic repaglinide with a label that includes the patented method will infringe the '358 patent. *See MedImmune, Inc.* v. *Genentech, Inc.*, 549 U.S. 118, 126-37 (2007). Novo's cases do not address this issue.

Finally, Novo confuses jurisdiction with the separate notion that this appeal could moot further proceedings below. Novo is free to argue to the District Court that issues of invalidity and unenforceability are moot if and when (a) Novo *loses* on appeal, (b) Novo corrects its misleading use code description, (c) FDA approves Caraco's ANDA with a section viii carve-out, and (d) Caraco receives summary judgment of non-infringement. Unlike in the cases cited by Novo, however, if Novo were to prevail in this appeal and FDA continued to reject Caraco's labeling carve out, the trial on these issues would have to go forward.

CONCLUSION

Novo's request for a stay of the underlying injunction pending appeal should be denied. But if the Court were to grant the stay, it should "remand[] the case to the district court to fix the amount of the

supersedeas bond pursuant to Fed. R. App. P. 8(a), while retaining jurisdiction over the appeal." *Gov't Guar. Fund of the Republic of Finland* v. *Hyatt Corp.*, 95 F.3d 291, 297 (3d Cir. 1996). And it also should expedite merits briefing as follows to avoid conflict with the October 14 trial in this case: Appellant's brief (October 12), Appellee's brief (November 2), and Appellant's reply (November 9). Novo has failed to explain any "emergency" need for an expedited briefing schedule if the Court denies the motion to stay.

OCTOBER 7, 2009

* * * *

[Signature Blocks and Certificate of Service Omitted]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Caraco Pharmaceutical Laboratories Ltd.	10/13/09
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
313 556 4178	(248) 926 0231
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. Licensee number if previously issued)*: 1150 Elijah McCoy Drive, Detroit, MI 48202	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(if previously issued)* 77-571

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Repaglinide Tablets, USP	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*: See continuation sheet 1

CODE NAME *(if any)*:

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	1 mg and 2 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Lowers the blood glucose in patients with type 2 diabetes mellitus (NIDDM)

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)*
☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (AMDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug: Prandin® Holder of Approved Application: Novo Nordisk Pharmaceuticals, Inc

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Amendment to Labeling amendment dated August 10, 2009.

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 **THIS APPLICATION IS** ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See continuation sheet 1
This site is ready for inspection

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See continuation sheet 2

[redacted]

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C0209318

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Correspondence to labeling amendment

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Robert Kurkowicz	Robert Kurkowicz. Sr. V P Regulatory Affairs	10/13/09

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1150 Elijah McCoy Drive, Detroit MI 48202	(313) 556-4105

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C0209319

Continuation Sheet 1 for FDA Form 356h

Amendment to Labeling Amendment for Repaglinide Tablets, USP, 1 mg and 2 mg

Chemical/Biochemical/Blood Product Name (*if any*)

The chemical name is S(+)2-ethoxy-4(2((3-methyl-1-(2-(1-piperidinyl) phenyl)-butyl) amino)-2-oxoethyl) benzoic acid

Establishment Information

1. **Drug substance**

Repaglinide, USP:

Sun Pharmaceutical Industries Ltd. Plot No. 25, Phase IV, G.I.D.C., Panoli – 394116, Dist. Bharuch, Gujarat, India	Drug substance manufacturer
Sun Pharmaceutical Industries Ltd. Acme Plaza, Andheri-Kurla Road Andheri (East), Mumbai - 400 059 India Contact: Mr. Ram Jhangiani Phone: +91-22-8230102, +91-22-8212128, +91-22-8212115 Fax: +91-22-8212010	Drug substance supplier

2. **Drug Product Manufacturer**

Sun Pharmaceutical
Industries Ltd.
270 Prospect Plains Road
Cranbury, NJ 08512

A] Drug product manufacturer
B] Packaging Site
C] Finished product and stability testing site

Contact: Mr. Jitendra Doshi,
Phone: 606 495 2802
FAX: 609 495 2711

Registration # 3005551493

Continuation Sheet 2 for FDA Form 356h

Amendment to Labeling Amendment for Repaglinide Tablets, USP, 1 mg and 2 mg

Cross References

DMFs referenced in the current application are as follows:

Company	**DMF #**
Sun Pharmaceutical Industries Ltd.	17825
Alpha Packaging (formerly Quality Container Co.) (for bottles)	6779
Cheveron Phillips Chemical Company, LP	1016
Ampacet Corporation	8394
Van Blarcom Closures, Inc. (for CRC closures)	5828
Ineos Olefins and Polymers USA (formerly Solvay Polymers)	3720
Sunoco Chemicals	1584
Ferro Corporation	6630
Polyone Plasitcs	15302

Unipac Corporation	3782
Mold Rite Plastics Inc. (for non- CRC closures)	16574
Phillips Sumika Polypropylene Company	10562
Sunoco Chemicals	1584
Selig Sealing Products, Inc.	4544
Kerr Group, Inc., a subsidiary of Berry Plastics (for CRC closures)	2256
Huntsman Corporation	9988
Plastics Color Corporation	12767
Selig Sealing Products, Inc.	4544
Berry Plastics, Inc. (for non- CRC closures)	5713
The Dow Chemical Company	12603
PolyOne	18859
Selig Sealing Products, Inc.	4544

CARACO
PHARMACEUTICAL LABORATORIES, LTD.

Regulatory Affairs

Amendment to Labeling Amendment

October 13, 2009

Kendra Stewart
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Document Control Room, Metro Park North 1
7520 Standish Place
Rockville, MD 20855-2773

Re: Amendment to Labeling amendment to ANDA for Repaglinide Tablets, 1 mg and 2 mg, ANDA No. 77-571

Dear Ms. Stewart:

This supplements our submissions dated August 10, 2009, and May 29, 2009, which address the May 6, 2009, use code change by Novo Nordisk Inc. and Novo Nordisk A/S (together, "Novo") for U.S. Patent No. 6,677,358 (the '358 patent) in reference to Prandin (repaglinide). In these prior submissions, we explained that Novo's new and vague use code description does not prevent Caraco from maintaining its section viii statement as to the '358 patent's method claim. This is because the entire record shows that Novo's patent does not cover the two uses of repaglinide for which Caraco seeks approval—i.e., as monotherapy and in combination with TZDs. *See Purepac Pharma. Co.* v. *Thompson*, 354 F.3d 877, 883-85 (D.C. Cir. 2004). We write to bring to your attention recent developments that further support Caraco's position.

As previously discussed, Novo has sued Caraco for patent infringement under the Hatch-Waxman Amendments in the United States District Court for the Eastern District of Michigan in connection with Caraco's ANDA. Following Novo's use code change on May 6, 2009, Caraco requested an injunction from the Court requiring Novo to correct its new use code description so that it accurately states that the '358 patent covers only one of the three approved repaglinide uses—i.e., the combination of repaglinide with metformin.

On September 24, 2009, the Court issued the enclosed decision that granted summary judgment to Caraco on this issue. Importantly, this decision makes clear what Caraco has consistently argued—namely, that the '358 patent does not cover the uses of repaglinide for which Caraco seeks approval (monotherapy and combination therapy with TZDs). The decision states in relevant part:

> The '358 patent which is the subject of this patent action does not cover repaglinide; it covers repaglinide only in combination with metformin. The U-968 use code narrative for the '358 patent states "a method for improving glycemic control in adults with type 2 diabetes mellitus." It is so broad as to incorrectly suggest that the '358 patent generically covers three (3) different FDA-approved methods of use of repaglinide:
>
> - monotherapy treatment
> - treatment in combination with thiazolidinediones
> - treatment in combination with metformin

> *However, Novo admits that the first two (2) uses are not covered by claim 4 of the '358 patent.*

9/24/09 Decision at 3 (emphasis added). The Court thus concluded: "The Patent Information submitted by Novo on its May 6, 2009 Form FDA 3542 for Prandin did not comply with the applicable FDA regulations and instructions, resulting in the U-968 use code that seriously misrepresents the approved method of use covered by claim 4." *Id.* at 4.

On September 25, 2009, the Court entered the enclosed injunction requiring Novo to correct its improper use code description by restoring the original description, which read: "use of repaglinide in combination with metformin to lower blood glucose." Novo must comply with this injunction within 20 days, but Novo has expressed an intent to appeal the injunction and seek a stay pending appeal.

In light of this judicial action by a Federal Court, FDA has no basis to rely on Novo's amended use code to reject Caraco's section viii statement. Caraco thus asks the Agency to approve its ANDA immediately, despite Novo's improper use code description. FDA does not need to, and should not, wait for Novo to change its use code description per the injunction because, as the Court's decision makes clear, *the '358 patent covers only the use of repaglinide in combination with metformin, and not the other two uses for which Caraco seeks approval.* In fact, as the decision notes, Novo has admitted this point. There can be no question that Caraco's section viii statement is entirely proper under these circumstances. *See* FDA ltr to Orescan and Hurst, FDA-2008-P-0343-0009 (12/4/08).

We would be pleased to answer any questions you may

have on this issue.

Sincerely,

/s/ Robert Kurkiewicz
Robert Kurkiewicz
Sr. Vice President, Regulatory Affairs

Enclosures

cc: Gary Buehler, R.Ph.
Martin Shimer
James F. Hurst, Esq.
Charles B. Klein, Esq.
David S. Bloch, Esq.

* * * *

[Enclosures Reproduced at Pet. App. 65a - 72a]

No. 2010-1001

IN THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Appellants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Appellees.

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE EASTERN DISTRICT OF MICHIGAN CASE NO. 2:05-CV-40188, JUDGE AVERN COHN

COMBINED PETITION FOR PANEL REHEARING AND REHEARING EN BANC

* * * *

[Signatures, Certificate of Interest, Table of Contents, Table of Authorities, and Circuit Rule 35(b) Statement omitted]

INTRODUCTION

Appellee Caraco seeks panel or en banc review of a splintered ruling raising issues of exceptional importance under the Hatch-Waxman Act—a ruling that each panel member recognized "tip[s] the [Act's] careful balance in the favor of pioneering manufacturers." Op. 12; Conc. 2; Diss. 23. Indeed, the majority's reading of the Act allows Novo to use its patent

to block Caraco from marketing drugs that Novo *concedes* do not infringe. This extraordinary result compels review, particularly in the context of a law designed to expedite, not delay, generic competition.

Here is the problem. When a drug has multiple uses and "a patent claims at least one, but not all, approved methods of using [the] drug," section viii of the Act expedites generic competition by allowing generics to "carve out" infringing uses from their product labels. Op. 4-5, 11. Caraco seeks FDA approval to market a generic version of Novo's drug for two uses that Novo admits do not infringe its patent. And every panel member agreed that Caraco has satisfied section viii.

Yet the majority held that Novo can block Caraco's product simply by providing FDA a description of its patent erroneously suggesting that it *does* cover Caraco's proposed use. After this suit began, and despite its repeated admissions in court, Novo did just that, submitting a newly broadened description of its patent to FDA. As the district court found, this submission "seriously misrepresents" the scope of Novo's patent. App. 4. But FDA does not independently determine the patent's scope; it relies on the brand's description of that scope, which is provided in the form of a "use code" and then listed in FDA's Orange Book. Thus, Novo's revised and admittedly overbroad use code led FDA to reject Caraco's "carve out" label, thwarting Caraco's effort to obtain FDA approval for non-infringing uses.

The issue is whether the Act provides a remedy for such abuse. It does. It authorizes counterclaims to "correct or delete the patent information submitted by the [patent] holder" when (1) there is "an approved

method of using the drug" that "the patent does not claim" (here, Novo's patent does not claim *two* approved methods of use), and (2) the "patent information" is inaccurate (here, Novo's use code admittedly misrepresents its patent's scope). 21 U.S.C. § 355(j)(5)(C)(ii)(I).

But over Judge Dyk's dissent—and contrary to the Act's text, structure, legislative history, and interpretation by FDA—the panel said Caraco has no remedy. Under the majority's view, (1) no counterclaim is available because Novo's patent claims *one* approved use, even though it "does not claim" two other "approved method[s] of use"; and (2) the counterclaim is effectively limited to *delisting* wrongfully-listed patents, even though the Act also refers to *correcting* patent information. Op. 13. Therefore, brands are now free to submit use codes at the highest level of generality—*e.g.*, "a method for treating diabetes"—thus extending their patents to non-infringing uses. And because overbroad use codes will thwart useful "carve out" labels, the ruling effectively writes section viii out of existence.

As Judge Dyk recognized, this "cannot be what Congress intended." Diss. 27. And if the law is to permit "manipulation of the Orange Book"—leaving generics "without any remedy" (*id.*)—that decision should come from the full Court, not from a ruling that split three ways and threatens the congressionally-mandated balance between brands and generics. Further review should thus be granted.

STATEMENT OF THE CASE

A. Structure of Hatch-Waxman Act

If a generic seeks to market a drug covered by an unexpired patent listed in FDA's Orange Book, "the

generic is generally required to certify that the patent . . . is invalid or will not be infringed by the sale or use of the [generic] drug." Diss. 3. This is referred to as a Paragraph IV certification.

The Act also provides, however, an alternative means of obtaining generic approval—the "section viii" statement. "Section viii addresses scenarios where a patent claims at least one, but not all, approved methods of using a drug." Op. 11. This provision is applicable when the Orange Book lists a method patent that "does not claim a use for which the applicant is seeking approval." 21 U.S.C. § 355(j)-(2)(A)(viii). Along with its section viii statement making that representation, "the generic manufacturer must submit a proposed label to the FDA that does not contain [*i.e.*, carves out] the patented method of using the listed drug." Op. 4.

Importantly, FDA does not interpret the scope of patents. So "[w]hen considering approval of [section viii] requests, the FDA relies on the applicable patent's use code narrative to determine the scope of the patented method." Op. 4. The use code narrative for each listed method patent is provided by the brand. Op. 3. "FDA approves the section viii statement only where there is no overlap between the proposed carve-out label . . . and the [brand's] use code narrative." Op. 4. Thus, accurate use codes are "essential to the [Act's] operation." Diss. 6.

B. Counterclaim Provision

In 2003, aware of brands' efforts to "block generic competition by making unwarranted claims to patent coverage" (Diss. 4), Congress enabled generic drug makers "in a Paragraph IV suit to assert a counterclaim challenging the accuracy of the 'patent informa-

tion' submitted to the FDA." Op. 5. As Congress provided:

> [The ANDA] applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) of this section on the ground that the patent does not claim either—
>
> (aa) the drug for which the application was approved; or
>
> (bb) an approved method of using the drug.

21 U.S.C. § 355(j)(5)(C)(ii)(I).

C. District Court Proceedings

In 2008, Caraco sought section viii approval for generic repaglinide, a diabetes drug that Novo markets as Prandin. "FDA has approved PRANDIN for three uses: (1) repaglinide by itself (*i.e.*, monotherapy); (2) repaglinide in combination with metformin; and (3) repaglinide in combination with thiazolidinediones ('TZDs')." Op. 5-6. Novo's patent claims repaglinide combined with metformin, but Novo "does not own patents claiming the other two approved methods." Op. 6.

Caraco's "section viii statement" thus "declar[ed] that Caraco was not seeking approval for the repaglinide-metformin combination therapy," and "FDA indicated that it would approve Caraco's proposed carve-out label." *Id.* But Novo then "updated its use code narrative for the '358 patent" (Op. 7) to indicate that its patent "encompass[ed] the use of repaglinide in monotherapy." Diss. 22. As a result, "FDA reversed itself and rejected Caraco's proposed labeling carve-out." *Id.*

Caraco thus filed a counterclaim, and the district court enjoined Novo to correct its use code, which was "so broad as to incorrectly suggest that [Novo's] patent generically covers three (3) different FDA-approved methods of use of repaglinide," when in fact "the first two (2) uses are not covered." App. 4.

D. The Divided Panel's Ruling

In a ruling that produced three opinions, the panel (Rader, Clevenger, Dyk, JJ.) reversed. First, reading the phrase "*an* approved method of use" to mean "*any* approved method of use," the majority (per Rader, J.) held that a counterclaim is available "only if the listed patent does not claim *any* approved methods of using the listed drug." Op. 10 (emphasis added). Second, the majority held that the term "patent information" in the provision is limited to "an erroneous patent number or expiration date" and "does not extend to the use code narrative." Op. 13.

In Judge Rader's view, a generic can use a Paragraph IV suit to prove that its "use will not overlap with . . . the patented use." Op. 11. But Judge Clevenger was "not as certain" of this "clean[]" result. Conc. 2. And although he blamed FDA for purportedly creating the confusion, he recognized that the outcome here risked "upset[ting] the careful balance of interests" reflected in the Act. *Id.*

Judge Dyk dissented, explaining that "the text is clear" in light of "the overall operation of the statute." Diss. 18. "[I]nterpreting 'an approved method' . . . to mean 'any' approved method," he noted, is "fundamentally inconsistent with the Supreme Court's admonition . . . that '[u]ltimately, context determines meaning.'" Diss. 16. And on the "patent information" issue, he explained that the majority's view was con-

trary to the text, "FDA's interpretation," and *Chevron*. Diss. 15.

Judge Dyk also disagreed with the notion that FDA caused "Caraco's predicament," citing Novo's admission that "FDA did not require [a change in the use code]." Diss. 23-24. But he agreed with Judge Clevenger that generics are "left without any remedy to correct an erroneous Orange Book listing" for a method patent, concluding that this "cannot be what Congress intended." *Id.* at 27.

POINTS OF LAW MISAPPREHENDED BY THE PANEL

The panel should grant rehearing. The lead opinion correctly notes that the context for this dispute is the "balance" that Congress sought to "strike" between "the pioneering and generic manufacturing interests." Op 12. But when concluding that its statutory construction did no violence to that balance, the lead opinion incorrectly assumed generics would still have a remedy, even without a counterclaim, via the "dispute resolution mechanism" of "Paragraph IV" litigation. Op. 11-12. That was an outright mistake, and the other panel members rightly took issue. Conc. 1; Diss. 26. FDA will *not* permit "carve out" labels unless it can determine, based on the brand's use code, that the revised label avoids an infringing use. Diss 22 n.17 (citing regulations). So where an overbroad use code precludes that determination, FDA requires the original, *infringing* label—thus eliminating the non-infringement defense and forcing the generic to prove *invalidity* to reach the market early. *Id.* And even more basically, Congress did not intend for Paragraph IV to be a substitute for section viii—it enacted both. Rehearing is needed to correct this

point of law, which the panel misapprehended.

REASONS FOR GRANTING PANEL OR EN BANC REHEARING

I. Rehearing is warranted because the panel's splintered decision rewrites a key provision of the Hatch-Waxman Act, in contravention of its text, structure, purpose, legislative history, and interpretation by FDA.

In addition to encouraging the gaming of Hatch-Waxman, the panel opinion rests on two key errors. *First*, it defies the text of § 355(j)(5)(C)(ii), which allows a counterclaim if there is "an approved method of using the drug" that the listed patent "does not claim." *Second*, it ignores FDA's reading of "patent information," which Congress ratified, and which warrants *Chevron* deference. These errors—on a recurring issue "essential to the [Act's] operation" (Diss. 6)—warrant review.

A. The majority misconstrued the Act's plain language and ignored the cardinal rule that statutory language must be read in context.

1. As countless decisions hold, "there is a basic difference between filling a gap left by Congress' silence and rewriting rules that Congress has . . . specifically enacted." *Lamie* v. *United States Trustee*, 540 U.S. 526, 538 (2004). Yet the panel changed the Act's text by "read[ing] 'an approved method' as 'any approved method.'" Op. 10 (quoting § 355(j)(5)(C)(ii)). That was simply wrong.

Novo admits there is "an approved method of using the drug" that its patent "does not claim." Yet the majority ignored this sensible reading of the plain text. Instead, it "detect[ed] no ambiguity" because,

"[w]hen an indefinite article is preceded and qualified by a negative, standard grammar generally provides that 'a' means 'any.'" Op. 10. But the fact that "an," when qualified by a negative, *can* mean "any" does not mean it *generally* means "any." Diss. 18 (citing *Webster's Third Int'l Dictionary* 1 (2002) and noting that the majority relies on secondary definitions of "an"). Congress instead chose "an," the meaning of which depends on what it is "followed by"—by its context. Diss. 18.

2. This is the deeper problem with the majority's decision: it ignores the "cardinal rule that statutory language must be read in context" (*Hawkins* v. *United States*, 469 F.3d 993, 1001 (Fed. Cir. 2006)), because "[u]ltimately, context determines meaning" (*Johnson* v. *United States*, 130 S. Ct. 1265, 1270 (2010)). Thus, "contextual indications may point clearly to one dictionary definition among conflicting alternatives." *Smith* v. *Brown*, 35 F.3d 1516, 1523 (Fed. Cir. 1994). By ignoring this possibility, the majority rewrote a vital provision of the Act.

First, the phrase "an approved method" appears in a provision entitled "[c]ounterclaim to infringement action," which places the burden of proof on the generic to show that "the patent does not claim" a certain method of use. By design, this provision asks not whether the *brand* can show that its patent *claims* "an approved method," but whether the *generic* can point to "an approved method" the patent "*does not* claim." "Only by such full reference to the context of the whole can [this] [C]ourt find the plain meaning" of the statute. *Smith*, 35 F.3d at 1523.

An illustration confirms this. Suppose A writes to B with news that she had a third child. In relating

the challenges of having three children, A adds that "my taxes are higher than they should be because I did not claim *an exemption*." Read in context, this statement does not suggest that A did not claim *any* exemptions—only that she did not claim an exemption *for the third child*. If B ignored the context and concluded that A did not claim *any* exemptions, we would not say A's use of the phrase "did not claim an exemption" was ambiguous. We would say B read it in isolation. The same is true of the panel's reading of "an approved method."

Second, to read "an" as "any" is particularly problematic given that "any" appears elsewhere in the same provision. *See* § 355(j)(5)(C)(ii)(II) ("any civil proceeding"). So "Congress knew how" to express other meanings. *See Central Bank* v. *First Interstate Bank*, 511 U.S. 164, 176-77 (1994). And as the bill's sponsor noted: "[T]o close the loopholes . . . the devil is in the details. . . . Change an 'and' to an 'a,' to a 'the' and you go from huge savings to huge costs." *Hrg. Before Cmte. on Judiciary*, 108 Cong. 15 (Aug. 1, 2003) (Sen. Schumer).

Third, section viii and the counterclaim provision work together and use similar statutory language—one refers to a patent that does "not claim *a* use" and the other refers to a patent that does "not claim *an* approved method." There is no reason to read these provisions inconsistently, as the majority did, such that one provision means "*any*" method (counterclaim) and the other refers to "*a*" use (viii).

Fourth, the Act allows counterclaims "to *correct or* delete patent information," § 355(j)(5)(C)(ii)(I), but the majority "render[ed] superfluous" the term *correct*. *See Astoria Fed. Sav. & Loan Ass'n* v. *Solimino*,

501 U.S. 104, 112 (1991). That is, brands may list only patents that claim the drug or an approved method of using it. § 355(b)(1), (c)(2). And in the majority's view, a counterclaim is available only where the patent claims neither one. But in those cases, the patent should not have been listed at all, and the only remedy is *deleting* all patent information. Indeed, under the majority view, even an incorrectly listed expiry could not be "correct[ed]," so long as the patent claimed the drug or any approved use. Op. 10.[1]

Fifth, the majority misread the counterclaim's legislative purpose—*i.e.*, to "close loopholes in the law and end abusive practices. . . by allowing a generic applicant, when it has been sued for patent infringement, to file a counterclaim to . . . *correct the patent information*." 149 Cong. Rec. 31200 (2003) (Sen. Schumer) (emphasis added). In the panel's view, the counterclaim was enacted only to fix the precise problem presented in *Mylan Pharm.* v. *Thompson*, 268 F.3d 1323 (Fed. Cir. 2001). But as Judge Dyk showed (at 10), the patent there did not belong in the Orange Book at all—a problem, as noted, that could have been solved by providing only for *deleting* patent information. In sum, "the majority's crabbed view of the statute sanctions an unjustified manipulation of the Orange Book." *Id.* at 27.

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[1] At argument, Novo asserted that a generic could file a counterclaim to "correct" typographical errors in a listed patent number. But a brand would typically have an incentive to fix such typos, and there is no reason to think Congress would create a *counterclaim for generics* to do so.

B. In violation of *Chevron*, the majority further erred in overriding the FDA's interpretation of "patent information."

The majority's ruling that the Act's reference to "patent information" is limited to "the patent number and expiration date," not "use codes," is also contrary to FDA's well-supported statutory interpretation—and thus violates *Chevron*.

As the majority noted, before Congress created counterclaims, "FDA promulgated a regulation [entitled '*Submission of Patent Information*'] . . . requir[ing] a [brand] to submit not only the patent number and the expiration date, but also the use code narratives." Op. 13-14. Congress thus acted "with full awareness of [FDA's] interpretation," and the majority's view ignores this "compelling evidence of legislative adoption of the agency's interpretation." Diss. 14-15, & n.11.

FDA's interpretation is correct. By filing a counterclaim, what a generic can "correct or delete" is "patent information submitted by the holder under [§ 505] (b) or (c)." § 355(j)(5)(C)(ii)(I). Because § 505(b) and (c) expressly mention only the patent number and expiry, the majority read "patent information" as limited to those items. But this rewrites the text by replacing the phrase "patent information *submitted . . . under* subsection (b) or (c)" with "patent information *referenced in* subsection (b) or (c)." In all events, the majority's ruling violates *Chevron* v. *NRDC*, 467 U.S. 837 (1984), which requires sustaining FDA's sensible reading of an undefined term: "patent information." Diss. 11-14.

In sum, the majority failed to see that "[s]licing a statute into phrases while ignoring their contexts—

the surrounding words, the setting of the enactment, the function a phrase serves in the statutory structure—is a formula for disaster." *Smith*, 35 F.3d at 1523. En banc review is needed to avert that disaster.

II. Left unaddressed, the majority's ruling will encourage Orange Book abuse, upsetting the Act's balance between brands and generics.

Contrary to the core purpose of the counterclaim, the panel's ruling invites "manipulation of the Orange Book." Diss. 27. Brands can now stymie marketing of admittedly non-infringing drugs by filing admittedly overbroad use codes. It is no overstatement to say that such brazen Orange Book abuse guts section viii, which allows FDA to approve generic entry "[i]f a method of using the approved drug is patented and is listed in the Orange Book, but the [generic] is not seeking approval for the patented use." *Allergan, Inc.* v. *Alcon Labs, Inc.*, 324 F.3d 1322, 1326 (Fed. Cir. 2003). The full Court's review is needed to prevent that result.

Judge Rader recognized that "a broad use code covering all uses of a pharmaceutical could require generic manufacturers to prove specifically that their use will not overlap with and infringe the patented use," dismissing this danger on the theory that Paragraph IV suits provide an "efficient dispute resolution mechanism" to resolve such issues. Op. 11-12. The other panel members rightly disagreed. Conc. 1 ("I am not as certain as Judge Rader that the ongoing Paragraph IV litigation will cleanly resolve the dispute between the parties."); Diss. 26 ("[T]he concurrence doubts that there is a remedy in the infringement suit, and I agree.").

A. As both the dissent and concurrence acknowledged, Paragraph IV litigation is ill-suited to resolve section viii issues.

First, it makes no sense to force generics to invoke Paragraph IV rather than section viii—the point of which is to *avoid* protracted litigation. "Paragraph IV certifications and section viii statements have quite different consequences. Applicants submitting section viii statements have no obligation to provide notice, nor must they wait thirty months for FDA approval." *Purepac Pharm. Co.* v. *Thompson*, 354 F.3d 877, 880 (D.C. Cir. 2004). Moreover, unlike Paragraph IV certifications, section viii statements are not an act of infringement and they are not subject to the 180-day exclusivity period for Paragraph IV applicants. *See Apotex, Inc.* v. *FDA*, 393 F.3d 210, 214 (D.C. Cir. 2004). Under the panel's 2-1 ruling, brands can force generics to make certifications they would not have to make—often delaying competition for 30 months—just by submitting overbroad use codes.

Second, if a generic cannot use a section viii carve-out label due to an overbroad use code, its label must discuss the patented use—inviting an infringement claim. This leaves just two paths to market, awaiting patent expiration or using a Paragraph IV certification to challenge the patent's *validity*. But neither option allows generics to litigate whether a carve-out label infringes, because FDA will not permit a carve-out label that raises any infringement issue. § 355(j)(2)(A)(v), (j)-(4)(G); 21 C.F.R. § 314.94(a)(8)(iv); Diss. 22 n.17. Thus, as Judges Clevenger and Dyk recognized, Paragraph IV suits provide no remedy for Novo's misconduct.

B. As the dissent correctly observed, the abuse enabled by the panel decision was not caused by the FDA.

Every panel member recognized that, in effect, this result "tip[s] the [Act's] careful balance in the favor of pioneering manufacturers." Op. 12; Conc. 2; Diss. 23. Judge Clevenger blamed FDA for the problem, evidently on the understanding that a change in the "approved labeling" for repaglinide required a change in its use code. Conc. 2. That is incorrect. The use code describes the patent, not the label. "[A]s Novo admitted," "FDA did not direct or request that Novo change its use code," "nor was [this] required under FDA regulations." Diss. 24. Rather, FDA "accepts at face value the use claimed by the patent holder." *Purepac*, 354 F.3d at 885. Thus, Caraco cannot ask FDA to correct Novo's overbroad use code.

CONCLUSION

By sanctioning Novo's conduct and leaving generics "without any remedy," the panel's split ruling invites the "true manipulation" of the Orange Book listings "the counterclaim provision was designed to avoid" Diss. 19, 27. Caraco is seeking to market a generic drug only for non-infringing uses. But Novo blocked that effort by broadening its use code and misrepresenting its patent's scope. This conduct renders section viii a dead letter, eviscerates the counterclaim's text and structure, and "cannot be what Congress intended." Diss. 27. Rehearing is needed to prevent that extraordinary result.

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MAY 14, 2010

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[Certificate of Service and Declaration of Authority Omitted. Addendum Reproduced at Pet. App. 1a - 52a]

CARACO
PHARMACEUTICAL LABORATORIES, LTD

Regulatory Affairs

GENERAL CORRESPONDENCE

May 26, 2010

Gary Buehler, R.Ph.
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Metro Park North 2 (room 286)
7500 Standish Place
Rockville, MD 20855

Re: General Correspondence to ANDA for Repaglinide Tablets, 1 mg and 2 mg, ANDA No. 77-571

Dear Mr. Buehler:

As you may know, the United States Court of Appeals for the Federal Circuit recently issued the enclosed decision that addressed the above-referenced ANDA involving repaglinide. We write to clarify that status of Caraco's patent certification in light of this decision.

As background, Novo Nordisk Inc. and Novo Nordisk A/S listed in the Orange Book U.S. Patent No. 6,677,358, among other patents, in reference to repaglinide, an oral anti-diabetic drug sold by Novo under the brand name Prandin. Claim 4, the sole method claim in the 5-claim patent, reads: "A method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin." Novo initially assigned the follow

ing "use code" to claim 4 that accurately characterized this patent claim: "U-546: USE OF REPAGLINIDE IN COMBINATION WITH METFORMIN TO LOWER BLOOD GLUCOSE."

In February 2005, Caraco filed its repaglinide ANDA asserting a paragraph IV certification as to all claims of the '358 patent. In August 2007, FDA tentatively approved Caraco's ANDA based on that certification.

Caraco expressed a desire to market a non-infringing repaglinide product after Novo's patent covering the repaglinide compound expired in March 2009. Thus, in April 2008, at FDA's suggestion, Caraco submitted a proposed ANDA amendment to assert a split-certification, which included a section viii statement for method claim 4 and a paragraph IV certification for the remaining product claims. Novo submitted a citizen petition challenging that split-certification.

On December 4, 2008, FDA rejected Novo's challenge. It ruled that Caraco could submit a section viii statement and carve out references to the patented metformin combination therapy from its label. *See* Docket Nos. FDA-2008-P-0343 and FDA-2008-P-0411. Later that month, Caraco submitted a proposed revised label removing all references to metformin-repaglinide combination therapy.

In May 2009, Novo amended the use code for Prandin to say: "U-968: A METHOD FOR IMPROVING GLYCEMIC CONTROL IN ADULTS WITH TYPE 2 DIABETES MELLITUS." The use code for PrandiMet (Novo's combination product), however, continues to use the original use code and thus de-

fines the specific method claimed by the '358 patent–i.e., the use of repaglinide in combination with metformin to lower blood glucose. FDA nonetheless orally notified Caraco that the agency would not approve a section viii statement with regard to claim 4 of the '358 patent in light of Novo's amended use code.

In August 2009, FDA formally characterized the proposed labeling carve-out as a labeling deficiency and said: "Please submit an updated patent certification addressing the 6,677,358 patent and its associated Use Code, U-968." FDA rejected Caraco's section viii statement presumably because it read Novo's new use code as extending the '358 patent's claims beyond the metformin combination therapy carved out of Caraco' s proposed label.

Caraco submitted letters to FDA dated May 29, August 10 and October 13, 2009, arguing that the entire record confirmed that Caraco can properly assert a section viii statement in its ANDA. While FDA never formally responded to these letters, our understanding is that the agency has rejected Caraco's position and continues to maintain that Caraco may not assert a section viii statement unless Novo reverts to its original use code for the '358 patent in reference to Prandin.

Caraco also sought, and obtained, a district court injunction requiring Novo to restore its original use code for Prandin. In a 2-1 decision, however, the Federal Circuit vacated that injunction. It held that Hatch-Waxman's counterclaim provision, 21 U.S.C. § 355(j)(5)(C)(ii)(I), does not permit Caraco to seek an injunction requiring Novo to correct its vague and overbroad use code description. Absent further action

by the Federal Circuit or legislative intervention, it appears that Caraco cannot obtain an injunction compelling Novo to provide FDA with a use code description that accurately characterizes the '358 patent. Novo has refused to correct its use code voluntarily because it knows that doing so will mean non-infringing, generic competition.

Given this background, it is Caraco's understanding that FDA has currently decided to reject the proposed section viii statement with regard to claim 4 of the '358 patent and, therefore, that FDA is now deeming Caraco's ANDA to contain a paragraph IV certification as of the time of tentative approval. Caraco appreciates that, depending on the resolution of the appeals process relating to the section viii issue, Caraco may ultimately need to maintain its paragraph IV certification as to all claims of the '358 patent to obtain final approval. However, it is currently maintaining that certification under protest. Specifically, Caraco has petitioned the Federal Circuit to rehear its decision vacating the injunction that would have required Novo to correct its overbroad use code description. If the Court of Appeals grants rehearing in the case and reverses its holding, Caraco will amend its patent certification to again make a section viii statement as to claim 4 and carve the patented use out of its label. Caraco also reserves its right to challenge FDA's decision as arbitrary and capricious.

Feel free to contact me if you have any questions at (313) 556 4105.

Sincerely,

/s/ Robert Kurkiewicz
Robert Kurkiewicz
Sr. Vice President, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Caraco Pharmaceutical Laboratories Ltd.	5/26/10
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
313 556 4105	(248) 926 0231
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 1150 Elijah McCoy Drive, Detroit, MI 48202	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*: 77-571

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Repaglinide Tablets, USP	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		CODE NAME *(If any)*
See continuation sheet 1		
DOSAGE FORM:	**STRENGTHS:**	**ROUTE OF ADMINISTRATION:**
Tablets	1 mg and 2 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Lowers the blood glucose in patients with type 2 diabetes mellitus (NIDDM)

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)*
☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug: Prandin® Holder of Approved Application: Novo Nordisk Pharmaceuticals, Inc

TYPE OF SUBMISSION *(check one)*
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APPENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
General correspondence

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See continuation sheet 1

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See continuation sheet 2

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* General correspondence

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Robert Kurkiewicz	Robert Kurkiewicz, Sr. V.P Regulatory Affairs	5/26/10

ADDRESS (Street, City, State, and ZIP Code)	Telephone Number
1150 Elijah McCoy Drive, Detroit MI 48202	(313) 556-4105

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

C0209295

Continuation Sheet 1 for FDA Form 356h

General Correspondence to ANDA for Repaglinide Tablets, USP, 1 mg and 2 mg

Chemical/Biochemical/Blood Product Name (*if any*)

The chemical name is S(+)2-ethoxy-4(2((3-methyl-l-(2-(1-piperidinyl) phenyl)-butyl) amino)-2-oxoethyl) benzoic acid

Establishment Information

1. **Drug substance**

Repaglinide, USP:

Sun Pharmaceutical Industries Ltd. Plot No. 25, Phase IV, G.I.D.C., Panoli - 394116, Dist. Bharuch, Gujarat, India	Drug substance manufacturer
Sun Pharmaceutical Industries Ltd. Acme Plaza, Andheri-Kurla Road Andheri (East), Mumbai - 400 059 India	Drug substance supplier

Contact: Mr. Ram Jhangiani
Phone: +91-22-8230102,
+91-22-8212128,
+91-22-8212115
Fax: +91-22-8212010

2. Drug Product Manufacturer

Sun Pharmaceutical Industries Ltd. 270 Prospect Plains Road Cranbury, NJ 08512	A] Drug product manufacturer B] Packaging Site C] Finished product and stability testing site

Contact: Mr. Jitendra Doshi,
Phone: 606-495-2802
FAX: 609-495-2711

Registration # 3005551493

Continuation Sheet 2 for FDA Form 356h

General Correspondence to ANDA for Repaglinide Tablets, USP, 1 mg and 2 mg

Cross References

DMFs referenced in the current application are as follows:

Company	**DMF #**
Sun Pharmaceutical Industries Ltd.	17825
Alpha Packaging (formerly Quality Container Co.) (for bottles)	6779
Cheveron Phillips Chemical Company, LP	1016
Ampacet Corporation	8394
Van Blarcorm Closures, Inc. (for CRC closures)	5828
Incos Olefins and Polymers USA (formerly Solvay Polymers)	3720
Sunoco Chemicals	1584
Ferro Corporation	6630

Polyone Plastics	15302
Unipac Corporation	3782
Mold Rite Plastics Inc. (for non-CRC closures)	16574
Phillips Sumika Polypropylene Company	10562
Sunoco Chemicals	1584
Selig Sealing Products, Inc.	4544
Kerr Group, Inc., a subsidiary of Berry Plastics (for CRC closures)	2256
Huntsman Corporation	9988
Plastics Color Corporation	12767
Selig Sealing Products, Inc.	4544
Berry Plastics, Inc. (for non-CRC closures)	5713
The Dow Chemical Company	12603
PolyOne	18859
Selig Sealing Products, Inc.	4544

* * * *

[Enclosure Reproduced at Pet. App. 1a - 52a]

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

Civil Action No.: 05-40188
Hon. Avern Cohn

BENCH TRIAL – VOLUME 5

Tuesday, June 8, 2010

* * * *

[Appearances Omitted]

* * * *

[*86]

consideration is copying by others of the invention. Novo has identified our ANDA and the ANDA to several other entities for repaglinide alone as proof that these entities all want to copy the patented combination.

As the Court is aware, our ANDA contains multiple efforts by Caraco to avoid identifying the combination in our labeling and so on. We believe the ANDA is relevant to that.

In addition, as the Court will recall, there was at one point an effort by Novo Nordisk to argue that the Court lacked jurisdiction over this case because we had attempted to carve out the combination therapy from our label. We wish to make sure the ANDA is in evidence so that in the event there is a dispute over jurisdiction, the ANDA, which, of course, is the core jurisdictional fact in the case --

THE COURT: They claim what, the Court lacked --

MR. BLOCH: Novo contended earlier on in this case that the Court lacked jurisdiction because Caraco attempted to carve out the --

THE COURT: Yeah, but Novo was the one that brought the suit.

MR. BLOCH: That is true. We do not believe they have justification.

THE COURT: They claim that the Court lacked jurisdiction, even though it's their complaint that initiated the suit?

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MR. BLOCH: That's what they contend.

THE COURT: Well, okay. Go ahead.

MR. BLOCH: So we wish to move into evidence DX 7, DX 145, DX 152 --

THE COURT: 145, 152.

MR. BLOCH: DX 292, DX 294, DX 295, DX 296, DX 299, DX 371, DX 372, and DX 373. Those are all communications with the FDA or, of course, ANDA itself.

THE COURT: Any objection?

MR. SITZMAN: Yes, Your Honor. There is not a sponsoring witness for any of those exhibits. Not a single witness in this case is testifying to the documents.

THE COURT: You dispute their authenticity?

MR. SITZMAN: Not their authenticity.

THE COURT: Are you disputing that they may arguably be relevant?

MR. SITZMAN: I dispute on the same basis that you first raised this issue, not relevant to an issue of validity or inequitable conduct in this case.

THE COURT: Well, are you then not going to claim in defense that anything in the ANDA is not relevant to the issue of validity or enforcibly?

MR. SITZMAN: That's our position, your Honor.

THE COURT: Well, in light of that stipulation, is there any need for these documents to be in the record?

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MR. HURST: Is there a stipulation that there won't be any challenge to jurisdiction as well? That would eliminate the need for the ANDA.

MR. SITZMAN: Well, first of all, I don't anticipate one.

THE COURT: No, don't tell me you don't anticipate one. This is -- I view this -- this is a straightforward patent suit in which the plaintiff claims infringement, which is conceded, and the defendant counterclaims on the grounds of invalidity and unenforcibility, period. That's the framework of what we're dealing with. Do you agree with that?

MR. SITZMAN: I do absolutely, your Honor.

MR. HURST: Your Honor, the only -- if there will be a challenge same day to jurisdiction --

THE COURT: There's no challenge to jurisdiction. The Court has jurisdiction. A district court has jurisdiction over patent cases. At issue in this case is the validity and enforcibility of the '358 patent, period.

MR. HURST: On the premise that there is no challenge to jurisdiction, we agree.

MR. SITZMAN: There is no challenge to jurisdiction.

THE COURT: Period.

MR. SITZMAN: Unfortunately, I can't give you a period. Let me just please --

THE COURT: Is there a period from what he said? You

[*89]

know, would you open your jacket a moment?

MR. SITZMAN: Sure.

THE COURT: I want to see if you wear a belt and suspenders because your answers to those questions suggest that you wear suspenders with your belt.

MR. SITZMAN: Your Honor --

THE COURT: Now I have a piece of sculpture in my office that shows the shirt and pants, suspenders and belt, but it also has the shirt sewn to the pants. I'm not going that far.

The question is, do you dispute that this Court has jurisdiction, yes or no?

MR. SITZMAN: I do not dispute at present.

THE COURT: No, not at present or in the future. I'm not -- come on. Don't play games with me.

MR. SITZMAN: Your Honor, I want to be candid. Let's be honest and candid, okay? There is a set of circumstances out there. It is beyond this Court's control where they have changed to an -- out of a Paragraph 4, which is vested this Court with jurisdiction to a Section 8.

There may be a later time down the road -- and I have a solution for the Court, too -- there may be a time later on down the road where somebody is looking back at this record saying this Court did not have jurisdiction.

My suggestion is if jurisdiction becomes an issue,

[*90]

then those documents come in. They -- there's not an issue today. This Court doesn't have an issue moving forward, and the documents should not come in today.

MR. HURST: May I, your Honor?

THE COURT: Sure.

MR. HURST: The simple solution is to put the ANDA in evidence, and that way we don't have to worry about the contingency argument that counsel just made. It is in evidence and --

THE COURT: It is in evidence. I agree with you. It's in evidence.

MR. SITZMAN: Can I ask one quick clarification? Can we have it in evidence for limited purposes? One of the things that I want to avoid is to have post-trial briefing that argues from documents to which witnesses have not testified. These documents are coming in -- should be coming in only for the limited purpose of jurisdiction.

THE COURT: No, I admitted them. They are authentic and arguably relevant under a limited set of circumstances. I doubt seriously if anyone will cite them in post-trial briefs or argument on the question of validity and enforcibility, but I'm not going to otherwise qualify them because unfortunately, I don't think at the level of the statute with regard to Hatch-Waxman.

MR. SITZMAN: Okay, your Honor.

* * * *

[*197]

THE WITNESS: Yes.

THE COURT: Are there occasions where a treating physician will prescribe metformin standing alone?

THE WITNESS: Yes, actually the first treatment by the guidelines.

THE COURT: Are there also circumstances where repaglinide is prescribed alone?

THE WITNESS: Not first choice.

THE COURT: I didn't ask first choice.

THE WITNESS: Very rare.

THE COURT: But it can be used as a stand-alone drug?

THE WITNESS: It can be.

THE COURT: It can be prescribed as a stand-alone drug?

THE WITNESS: Yes.

THE COURT: I don't have anything further. We are in recess until 9:00 tomorrow morning. Caraco used two and half hours and Novo used two hours.

You have a safe trip.

THE WITNESS: Thank you, very much.

(Proceedings adjourned at 4:31 p.m.)

* * * *

[Certification Omitted]

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

Civil Action No.: 05-40188
Hon. Avern Cohn

TELEPHONE CONFERENCE

* * * *

[Appearances Omitted]

[*2]

Detroit, Michigan

Monday, September 13, 2010

2:35 p.m.

THE COURT: Give your appearances to the reporter.

MR. SITZMAN: It's Mike Sitzman and Wayne Barsky for the Plaintiffs Novo Nordisk A/S and Novo Nordisk, Inc.

MR. KLEIN: Charles Klein for Defendants Caraco and Sun.

THE COURT: All right. This call apparently is a

follow-up to my email to you of September 7th, in which I said:

> "Over the weekend I reviewed the papers relating to Caraco's motion for protective order, Document 481. I do not understand the nature of the dispute relating to the motion. This is the first time I have seen Magistrate Scheer's order, Document 62. I know nothing of its background. At the time it was entered the posture of the case was far different than today.
>
> "Second, my understanding of the case today is that it has gone forward on Caraco's counterclaim of patent invalidity and unenforceability. This claim, while prompted by the difficulties Caraco is having with the FDA over approval of its ANDA, does not involve proceedings in front of the FDA.
>
> [*3]
>
> "Third, Caraco can always ask for a protective order on any documents it produces in this case. What was previously vacated was a blanket protective order. Perhaps a conference call can clear up my lack of understanding of what is involved in this motion for a protective order."

Have I got it right?

MR. SITZMAN: That's the email that you sent us, Your Honor.

THE COURT: Right. So what am I doing with a protective order that I don't understand why Novo would want documents that Caraco would not produce, doesn't want to produce, and then Caraco say-

ing if it produces the documents they will be spread all over the public record while Caraco can always ask for a protective order to limit use of documents?

MR. KLEIN: Your Honor, this is Chuck Klein. May I explain the nature of the motion?

THE COURT: Yeah, sure.

MR. KLEIN: Okay. Well, Novo -- before we filed the motion Novo made a demand for all FDA correspondence concerning Caraco's ANDA. For example, Novo asked for documents concerning where repaglinide will be manufactured, and they also want documents concerning a dispute with another generic company about whether Caraco's tentative approval from the FDA was timely. Our position is that these documents are

[*4]

completely irrelevant to the case. The Court has already struck all ANDA documents from the trial record at Novo's request on the grounds that they were irrelevant.

Now that Novo has filed a motion to dismiss for lack of jurisdiction, we agree that documents with regard to Caraco's patent certification or label are relevant to that motion, and we produced all of those documents. So we believe that's the end of our obligation under Rule 26(e) because none of these other documents that they are seeking are even arguably material, let alone, let alone material as covered by Rule 26(e) and thus they have no right -- Novo has no right to compel the production of those documents and we have no obligation to produce them. So that's where we stand today.

THE COURT: Well, in other words, you are saying they want these documents in relation to the motion to dismiss for lack of jurisdiction?

MR. KLEIN: Well, not exactly. We gave them the documents --

THE COURT: Wait a minute.

MR. KLEIN: Yes, yes. Forgive me, Your Honor. I think that is the nature of their request. I'll let them speak for themselves.

THE COURT: I understand, but Magistrate Judge Scheer's Notice to Produce, Document 62, had nothing to do with this jurisdictional question. I don't know what was going on

[*5]

when that order was entered. The case was still in front of Judge Gadola.

MR. KLEIN: That's right, Your Honor.

THE COURT: So it seems to me that -- well, let Novo speak.

MR. SITZMAN: Well, Your Honor, thank you, it's Mike Sitzman. When Magistrate Scheer entered his order, the case was in an early discovery phase, and Caraco had not produced communications it had had with the FDA concerning the ANDA. And Magistrate Scheer, as you can see, ruled that they needed to produce all of the ANDA-related documents, the submission itself, any additions, deletions --

THE COURT: I know. All right. Mr. Sitzman, let's make it easy. I'm going to vacate Magistrate Judge Scheer's order. I didn't appoint him. I didn't refer anything to him. I don't want to go back there.

As of today they want a protective order. Now, what is it that you want as of today that they have not produced and why? I mean that's the easiest way to deal with this.

MR. SITZMAN: Your Honor, the motion to dismiss, as Mr. Klein said, relates to, and this case, is premised on their ANDA, and their ANDA is what is filed with the FDA. And all of the communications, the motion to dismiss is premised on the fact -- and you now have a fully briefed motion on this -- is premised on the fact that they do not have a Paragraph IV

[*6]

certification. And they have had a number of communications with the FDA that have gone over the course of two and-a-half years where they have gone back and forth over their Section viii certification. They have tried to carve things out of the label --

THE COURT: I know all of that.

MR. SITZMAN: Well, but that is the crux of the motion to dismiss because, Your Honor, and I don't think this is a surprise, if you have looked through the briefs there is no case law out there, there is no authority that allows the courts to continue forward in a case where there is just a Section viii to the patent claim at issue.

THE COURT: All right. I have a suggestion for you. I have a series of questions I'm going to ask that may explicate this, okay? It seems to me that Caraco was premature in asking for a protective order. Better, they should have asked -- better, you should have filed a notice to produce and they should have refused to produce it and then you should have filed a motion

to enforce production, and then we would have a proper dispute over the discovery. It just seems to me more logical. In other words, the horse got before -- the cart got before the horse or something. There's an analogy there.

So I understand what you're saying, and it may be that in the questions I'm about to ask this will be clarified. So if you will indulge me for a moment, I will address the

[*7]

motion to dismiss, okay, and I think this will clarify things.

These are my questions. First, does the joint appendix that was recently filed cover all of the documents relevant to the motion to dismiss?

MR. SITZMAN: Can I jump in, Your Honor, or do you want to read the rest of the questions?

THE COURT: No, that's the first question. Initially when you filed the motion to dismiss you filed some documents.

MR. SITZMAN: Right.

THE COURT: Then when Caraco answered a joint appendix of documents was filed. So does that mean that the joint appendix of documents are the documents relevant to the motion to dismiss and Caraco's response to the motion to dismiss?

MR. SITZMAN: It contains all of the documents that we know about and that we have. That's the reason for the protective -- that's the reason why we asked, and Caraco has admitted, that they are withholding documents that we have not seen.

THE COURT: Okay, but I can ignore that first book of documents?

MR. SITZMAN: Yes, you can ignore that. If that's the question, you can ignore the first book of documents.

THE COURT: All right. That's number one. Number two, only Novo has filed a book of cases. I

[*8]

take it this book of cases that Novo has filed are all of the cases relevant to the motion so far as Novo is concerned, case law.

MR. SITZMAN: Those are the key authorities that we have filed that Novo believes are relevant.

THE COURT: All right. Caraco has not filed a book of cases.

MR. KLEIN: If we haven't -- I thought we had, but if we haven't --

THE COURT: If you have, you better tell me where it is because Julie has not given it to me.

MR. KLEIN: Okay. I'll look into that. If it hasn't been filed, then it will probably --

THE COURT: It doesn't have to be filed. It has to be lodged.

MR. KLEIN: Lodged, I'm sorry.

THE COURT: Four. I take it there is nothing in the complaint and answer and in the counterclaim as amended that bears on the motion except as are included in the joint appendix?

MR. SITZMAN: No, I don't think that's entirely correct, and maybe I don't understand the question,

Your Honor. The complaint that we filed, that Novo Nordisk filed that initiated this action was premised on a Paragraph IV --

THE COURT: I know. I understand.

[*9]

MR. SITZMAN: That's the allegation that's in there so that the relevance there is that that allegation is no longer and has no vitality. It's a set jurisdiction in this case.

THE COURT: All right. Well, what you are saying is it no longer has vitality because Caraco also filed a counterclaim that says the patent is invalid.

MR. SITZMAN: They did do that subject to the court -- pending jurisdiction in the court.

THE COURT: Well, why couldn't they have -- well, the thought just enters my mind, given the posture of everything why couldn't -- since the patent, the patent is an impediment to the ability of Caraco to get FDA approval, why couldn't it have filed as an original action a suit to invalidate the patent?

MR. SITZMAN: Your Honor, they couldn't.

THE COURT: Why couldn't they?

MR. SITZMAN: Because the Declaratory Judgment Act is very specific. It limits cases and controversies involving drug patents to those that are enumerated within the Hatch-Waxman statute, and if it doesn't exist, it was in the Hatch-Waxman statute, there is no case or controversy and there is no Article III jurisdiction for this court to have heard a freestanding declaratory relief case or counterclaims for declaratory relief.

[*10]

THE COURT: Well, let me ask you this, Mr. Sitzman. If I want to go out in the market and market something and I know there is someone that owns a patent who is going to assert that patent against my ability to market it, why can't I sue them claiming their patent is invalid? Where does Caraco go to find a forum that will adjudicate the validity of your patent?

MR. SITZMAN: The Federal Circuit -- you asked two questions. Let me answer the last one first. The Federal Circuit answered that last question, which was the Federal Circuit made clear that in order for them to adjudicate the validity of our patent in the context of this dispute they needed to file a Paragraph IV certification so that that issue could be decided.

Your first question is why couldn't you just go into the market or file a lawsuit knowing that somebody was going to come and assert a patent. The Hatch-Waxman Act preempts that. That's what Congress did. They created this balance, this artificial act of infringement that would test these patents only in the situation where a Paragraph IV certification existed. If they didn't file a Paragraph IV, there would be no jurisdiction. Remember, this is not an ordinary patent case where there is a product that is on the market. This is a case in which, in which they have not launched a product and they are relying on a congressional statute that creates jurisdiction.

[*11]

THE COURT: Okay. I understand what you are saying. Let me go on a minute, and I'll get back to you.

MR. SITZMAN: And one more important point, Your Honor, which is it is akin, it is akin, it is exactly like asking the Court for an advisory opinion, which you know is absolutely per se prohibited. By asking the Court to get involved and decide whether pre-launch of a drug that doesn't qualify under the Hatch-Waxman statute, they are asking you for pre-approval, before the drug is approved, they are asking for an advisory opinion from this Court as to whether the patent is invalid and/or not infringed, and that is not permitted under the Hatch-Waxman statute. It's not permitted under the Article III case law --

THE COURT: So they have to get -- your position --

MR. SITZMAN: -- or Declaratory Relief Act.

THE COURT: So they have to get FDA approval of the drug before they can sue for validity of the patent?

MR. SITZMAN: If they are going to maintain a Section viii statement. If they are going to switch to a Paragraph IV, that will invoke the jurisdiction of the federal courts. But that is the, that is the difference. If they are currently in a Section viii statement, they do not invoke the jurisdiction of these courts. If they get approval for their drug, then they can launch and then there will be a patent infringement suit, but if they want to adjudicate this issue

[*12]

before approval and before they launch, they have to have a Paragraph IV certification.

THE COURT: All right. Let me ask -- did you want to say something, Mr. Klein?

MR. KLEIN: Well, there were many misstatements in what Mr. Sitzman just said. If the Court wants to hear explanations, I'm happy to give them.

THE COURT: Well, I'll get there in a moment.

MR. KLEIN: Okay.

THE COURT: As I understand it -- wait. Initially Novo filed a motion to dismiss, Document 92, and Caraco filed an opposition, Document 102, and then in Document 107 Novo withdrew its motion to dismiss and it said, "In light of the actions taken and the guidance provided by the Court during an in chambers conference on July 29." That in chambers conference on July 29 was not on the record, was it?

MR. SITZMAN: It was not, Your Honor. That was our first meeting with you.

THE COURT: So I don't know what I said.

MR. SITZMAN: Let me remind you, if you don't mind, Your Honor.

THE COURT: Yeah, fine. I want you to.

MR. SITZMAN: Okay. Thank you.

There were a number of pending motions that we had in front of Judge Gadola at that time, and Your Honor said to us

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that for the first time in this case we finally had a judge in this matter that was going to take over this case, and at that time you immediately denied two or three of our motions. You ordered a bunch of depositions to take place immediately. You ordered us to produce and make available certain European witnesses either in Europe or in the U.S. You set a trial

date for six months later, and in the face of the jurisdictional motion you said to us something very similar to what you said the other day on the phone, which is you said I don't think this has any basis at all, you brought the case, you filed the patent infringement case, I don't understand why you would move to dismiss it, I can't believe this would have any merit.

THE COURT: And what did you say?

MR. SITZMAN: And then you said I would strongly advise that you withdraw it, and we said, Your Honor, we would be happy to look at it. And you were very -- you know Your Honor gets very, very stern, you know.

THE COURT: I know.

MR. SITZMAN: And you said very pointedly in front of all of our colleagues that -- I don't know if the Rule 11 issue had been mentioned, but you certainly suggested that you would not pursue this motion. You told us that we should consider and withdraw it. We did do that without prejudice, as you know, shortly after that.

THE COURT: All right. So what you are saying is I

[*14]

intimidated you into withdrawing it and then you allowed the case to go forward and each of you spent a couple of million dollars and after you got done with all of that you decided to renew it?

MR. SITZMAN: Yes, Your Honor is partly correct. We did, but we continued to raise this. Every

time they filed a motion for summary judgment we raised this jurisdictional motion every single time.

THE COURT: Until everybody spent a lot of money, and then you bring it back.

MR. SITZMAN: Well, Your Honor, look, I understand the concern that you are raising, but remember, the situation we were facing with Your Honor and Your Honor's advice and we preserved the jurisdictional motion --

THE COURT: I know, I know, I know.

MR. SITZMAN: It cannot be waived. It cannot be cured.

THE COURT: All right, okay. We'll get back to that. Thank you.

All right. If Caraco had filed an ANDA with a Section vii statement and received FDA approval, Novo could have sued Caraco for infringement and Caraco could have filed a counterclaim for infringement. Is that a fair statement?

MR. SITZMAN: It's a fair statement. I presume you meant Section viii.

[*15]

THE COURT: Section viii, yes.

MR. SITZMAN: If they filed a Section viii and got approval for Section viii and launched, we would file a regular patent infringement suit and they could file a counterclaim for declaratory relief at that time.

THE COURT: All right. Now, as things stand now, does the '358 patent stand as a barrier to Caraco getting approval of its ANDA?

MR. SITZMAN: No. Sorry, I was moving closer to the microphone. That may have come out a little loud.

THE COURT: What do you say, Mr. Klein?

MR. KLEIN: Well, the -- we have to get past that patent or else we will be sued. I don't believe the '358 patent itself is stopping the launch because there's no preliminary injunction.

THE COURT: Well, but is it a barrier to the FDA approving your ANDA?

MR. KLEIN: The '358 patent is a barrier to -- I don't believe it's a barrier to FDA approving the ANDA, but it's a barrier to FDA approving the Section viii statement. Do you need me to clarify that?

THE COURT: Yeah.

MR. KLEIN: Okay. We applied, as the Court knows, to market repaglinide with a label that did not include the metformin-repaglinide combination. Because of the '358 patent,

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Novo was able to list it in the Orange Book along with its use code narrative. Because of the overbreadth of the use code description, the FDA is now preventing Caraco from proceeding with the label that it proposed, which was pursuant to Section viii. So what Caraco did was it, after the Federal Circuit vacated the injunction, it told the FDA that it's no longer proceeding with Section viii, that it's maintaining the Paragraph IV certification that it's had on file throughout this litigation, and its label will now include the patented combination.

The '358 patent is not blocking the FDA from approving that ANDA as it now stands, but once we launch or -- I mean Novo has an infringement claim now because we have stipulated to infringement, and if Novo were to maintain or prevail on this action, they could then get an injunction to stop the launch.

MR. SITZMAN: Your Honor?

THE COURT: Wait a second.

As I understand it, maybe I'm wrong, Novo says Caraco initially filed a Paragraph IV certification with respect to Claim 4 of the '358 patent. Caraco amended its ANDA and withdrew the Paragraph IV certification and replaced it with a Section viii statement. Isn't that what Novo is really saying? Because when Novo started the lawsuit back in antiquity it started it on the basis of Caraco filing a Paragraph IV

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certification with respect to Claim 4 of the '358 patent, and then it says, as I understand it, Caraco amended its ANDA and withdrew its Paragraph IV certification and replaced it with a Section viii statement. Isn't that what Novo's essential position is?

MR. SITZMAN: Yes, Your Honor, that is correct.

THE COURT: Okay. Now --

MR. KLEIN: We disagree with that characterization.

THE COURT: Well, wait a second.

MR. KLEIN: Okay.

THE COURT: If that's the case, while I know it's in the papers, I would like identification of the exhibit which expressly displays these actions. Which exhi-

bit shows Caraco filing the Paragraph IV certific tion, and which exhibit displays Caraco amending tl ANDA and withdrawing the Paragraph IV certific tion and replacing it with a Section viii statement?

Wait a second. Also, now I have a question. H the FDA approved this change in the ANDA from Paragraph IV certification to a Section viii stat ment?

MR. KLEIN: No, of course it has not. That's wl we went to trial.

THE COURT: Is the FDA treating the ANDA : having a Section viii statement only?

MR. KLEIN: No.

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MR. SITZMAN: Yes.

MR. KLEIN: No, it is not, Your Honor.

THE COURT: Well, that's, that's, that's whe we really -- the nub of this dispute. Novo initial filed suit and stated the Court had jurisdiction and now moving to dismiss the case because of the a sence of jurisdiction. Novo is saying the Federal Ci cuit said Caraco can't proceed -- on the other han Novo said Caraco can't proceed by way of a Secti viii statement and the FDA says Caraco cannot -- n I think the FDA also says Caraco can't proceed l Section viii.

MR. KLEIN: Correct.

THE COURT: So as long as there's an ambigui in Caraco's position before the FDA, whether it's pr ceeding under Paragraph IV or proceeding under Se tion viii, and apparently, according to Caraco, i been unable to eliminate the Paragraph IV becau

the FDA says you are proceeding under Paragraph IV, why isn't there jurisdiction? Now we got down to the nub of all of this.

MR. SITZMAN: Well, Your Honor, the last statement, you probably heard me interject there, is a wrong statement, and you need not look any further than what Caraco said to you in their statement of undisputed facts in support of their motion for summary judgment, which is Exhibit 8. They told you, they told the Court and they explained to the Court that the ANDA contains a certification under Section viii that --

[*19]

under -- that they have a Section viii statement as to Claim 4. That's -- they moved for summary judgment on that basis, Your Honor. What they are trying to do now is they are trying to reconstruct what they previously said and admitted to the Court as a way of trying to save jurisdiction in this case, and, Your Honor, that is not right.

What you heard -- you asked the right question of Mr. Klein, and he admitted to you, he told you that the '358 patent is not an impediment to FDA approval. The only impediment to FDA approval right now is Caraco's refusal to convert back to a Paragraph IV and clear up all of their GNP problems, which is a separate issue altogether. But the patent is not an impediment. The patent is doing nothing, and that's why they cannot launch. It has nothing to do with the patent.

And what Mr. Klein did was he admitted to you that what he's seeking here and what this trial was all about is an advisory opinion that if in the future when they launch they will then have an advisory

opinion of what will happen when an infringement suit can be brought. That is not a proper role for an Article III court, and to hear Mr. Klein tell you that they do not have a Section viii is an absolute falsehood given all of the filings that they have made in this court saying time and time and time again that they have filed a Section viii repeatedly over and over and over again.

And the Federal Circuit, the Federal Circuit picked

[*20]

up on this very point and in their case explained that Caraco submitted -- I'm reading from the opinion.

> "Caraco submitted an amended ANDA with a Paragraph IV certification for the '358 patent and a Section viii statement declaring that Caraco was not seeking approval for the repaglinide-metformin combination therapy."

It's in the Federal Circuit's opinion because it was in Caraco's briefs that they submitted to the Federal Circuit. And what they are doing now is they are trying to quickly backpedal trying to get you to find some ambiguity so you can sort of save jurisdiction when jurisdiction doesn't exist.

MR. KLEIN: Your Honor, may I respond to that?

THE COURT: Yeah. You better make a very complete response because I don't want to comment on Mr. Sitzman, but it seems to me he's saying that at one time back in August '08 -- no, at a conference on July 29, '08 the Court intimidated him and it's taken more than two years for him to shake off that intimidation and get courage enough to come back and claim no jurisdiction and for two years he's been

under this pressure from the Court not to claim no jurisdiction.

Mr. Sitzman, I have to tell you, that's the way you are coming across. That you finally, finally came to grips and were able to assert no jurisdiction to the Court, and all of these last two years and while we spent all of this time in

[*21]

this validity case you were chafing, afraid of the Court, which is very flattering to me, but I don't think that's what I really meant or intended. Anyhow -- and if I did intimidate you for those last two years, I apologize.

Go ahead, Mr. Klein.

This is fabulous. This whole conversation is fabulous.

MR. KLEIN: I find it borderline humorous that Mr. Sitzman is accusing me of backpedaling, and I certainly didn't admit to the things he claimed I admitted. He's exaggerating.

THE COURT: Well, I did read this Paragraph viii, I must tell you. "As amended in April 2008, this ANDA contains a certification under 21 U.S.C.," da da da da da, "that Claims 1, 3 and 5 are invalid or will not be infringed. It also contains a statement under 21 U.S.C. 8 that use Claim 4 does not claim a method of use for which Caraco is seeking approval."

So I don't know what all of that means.

MR. KLEIN: Let me back up and give the Court the history. We filed a Paragraph IV certification that was not specific to any claims at the outset and

then gave Novo notice. Novo sued. There is no dispute there was jurisdiction at the outset of this suit.

THE COURT: Okay, because you did not designate a particular claim?

[*22]

MR. KLEIN: Correct.

THE COURT: Okay. Go ahead.

MR. KLEIN: It was a Paragraph IV all claims, and there was jurisdictions. Novo sued. There is no dispute about any of that. The dispute occurs when we attempted to amend our ANDA to include a Section viii statement, and that happened I believe in or about April 2008.

When that happened, there were two different cross-motions. We filed a motion for summary judgment asking the Court to grant a summary judgment on the ground that our ANDA was not going to infringe because of the Section viii statement. Novo filed a motion for a preliminary injunction saying -- telling the Court ignore the Section viii statement because the FDA hasn't approved it yet and the FDA may never approve it. What happened was the day before the preliminary injunction hearing Novo withdrew its motion, and with regard to our motion for summary judgment, the Court held that in abeyance on the ground that it was unclear what the FDA was ultimately going to do. This was all before the use code change, right?

So the case was going forward on the ground that we attempted to amend our ANDA to include a Section viii statement, but it was unclear how the FDA was going to deal with that. In other words, we did

try to move the case. We tried to move the case by redacting the patented information

[*23]

from the label. Then Novo took steps in May 2008 to prevent us from moving the case, and that's when they amended their use code, which then triggered a whole host of events that ultimately resulted in the FDA saying you cannot include a Section viii statement in your ANDA.

Now, getting back to one of the Court's questions, which is, what do the regulatory documents say? Putting aside how Caraco characterized them and how Novo characterized them, the regulatory documents, the first Paragraph IV certification was a plain Paragraph IV certification, not specific to any claim. In April of 2008 -- and I can direct the Court to the exhibits. I can send an email. I don't have them handy, but there are just two exhibits, I believe. The first is the original Paragraph IV certification, which is not claim specific, and then in April 2008 we included virtually the identical Paragraph IV certification, it still was not specific to any claim, but then we also included a Section viii statement which was specific to Claim 4.

Then we went through that whole counterclaim injunction, the Federal Circuit appeal, and the Federal Circuit vacated this Court's injunction and the FDA made it clear that they were not going to approve the Section viii. So we sent a letter in May 2008 to the FDA confirming what we believed to be obvious to all parties, which is that we can no longer proceed with the Section viii.

[*24]

So we are now proceeding with our Paragraph IV certification, which has been part of the regulatory record throughout the course of this litigation, and our label will in fact contain the patented use, which we have stipulated will infringe the patent, and that's why we went to trial. We went to trial to prove that the patent is invalid and unenforceable, and once we hit the market with our label, it will not be infringing the '358 patent. So when you asked if the '358 patent was an impediment to the FDA approval, technically no, but it is an impediment to a launch if you say it's valid because we have stipulated to infringement.

This is all consistent with the regulatory and statutory scheme with regard to Hatch-Waxman. We had a Paragraph IV and there was jurisdiction, unlike in the *Mylan* case, and we attempted to moot the case with the Section viii, but the case was never mooted. The only way the case would have been mooted is if the FDA had actually approved our Section viii statement, which never happened. And that's exactly the argument that Novo made to Your Honor in connection with their motion for preliminary injunction, and it's consistent with Supreme Court precedent and it's consistent with common sense. We are attempting to market an infringing product. Under the Hatch-Waxman Act that is a statutory act of infringement.

Section 271(e) does not talk about Paragraph IV. It

[*25]

says if you want to try to market a product that arguably infringes a patent the Court has jurisdiction. We think that ends the inquiry.

THE COURT: Wait, Mr. Sitzman. I don't think you should respond at this moment.

Let me tell you what this discussion explicates. It explicates that there is a factual dispute which underlays Novo's claim that there is no jurisdiction, that that claim of lack of jurisdiction requires resolution of a factual dispute as to whether or not there is still a -- hold on a minute, I want to get the language correct -- a Paragraph IV certification application pending before the FDA because if there is a Paragraph IV certification pending before the FDA there is clearly jurisdiction, and Novo seems to say that the only thing before the FDA is a Section viii statement. Caraco says that's not true, there is a Paragraph IV certification before the FDA, and that's why there is jurisdiction.

Caraco apparently is not claiming there is generic jurisdiction of this Court to treat Novo as threatening in the classical terms of patent law, threatening to bring an action and therefore the putative infringer in anticipation of that jumps in with a declaratory judgment and then you get this whole hassle of whether there is really a threat, there is not a threat, and whether sufficient action has been taken by the patent owner to allow for jurisdiction.

[*26]

I think it important, notwithstanding all of this paper that has been filed and these books, for Caraco to file a statement of material facts not in dispute justifying jurisdiction in the court under Hatch-Waxman because of the Paragraph IV certification that's pending before the FDA, and Novo can contest that statement because if there's an ambiguity as to whether or not there is a Paragraph IV certification pending before the FDA there is jurisdiction.

MR. KLEIN: Your Honor, I'm sorry, you did make a comment saying that we weren't asserting jurisdiction under the Declaratory Judgment Act. We are --

THE COURT: I know you are, but you are invoking the Declaratory Judgment Act as, part of it, based upon the fact that there is a Paragraph IV certification pending before the FDA.

MR. KLEIN: It's more than that, Your Honor.

THE COURT: Well, whatever. What you ought to do is give me a statement of material facts so that I don't have to tease them out of why there is jurisdiction.

MR. KLEIN: All right. We'll do that, Your Honor.

THE COURT: Well, am I wrong in that's what I need?

MR. SITZMAN: Your Honor, it's Mike Sitzman. May I respond real quickly?

THE COURT: But first does anyone dispute that there is a factual dispute here?

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MR. SITZMAN: Well, I disagree that a factual dispute even if it existed, and I beg that question because I don't think one exists, but even if a factual dispute existed it still would not be enough basis for this Court to establish jurisdiction. Keep in mind how the Court has to establish jurisdiction, and it is Caraco's burden, you are right about that, but unless they can establish that that jurisdiction clearly exists, there is no jurisdiction. So the fact that we have a situation where the Court is leaning towards a disputed fact demonstrates that there can't be jurisdiction.

THE COURT: No, Mr. Sitzman, you've got to remember that you are the one that filed the complaint and you are the one that asserted there was jurisdiction because you said that Caraco had filed an ANDA with a Part IV certification. You said that in your original complaint and amended complaint. So you are the one that asserted it, and now you are saying that there has been a change in the factual predicate for jurisdiction.

MR. SITZMAN: Correct, but keep in mind I'm not the one asserting these claims. The claims that are at issue right now, according to the Court and according to Caraco, are Caraco's counterclaims. Caraco bears the burden to establish jurisdiction.

THE COURT: No, it doesn't because it conceded infringement. So you won your lawsuit. You won your lawsuit.

[*28]

You said they were going to infringe. So you won it, and they counterclaimed.

Whatever it is, I want the statement of material facts from Caraco first. I don't like to keep prolonging this and prolonging it, but it's now clear because it's that statement of material facts that you claim you can't get your hands on, that's why you want this discovery against Caraco.

MR. SITZMAN: That's true, Your Honor. That is absolutely true. Now, the one thing I want, I want to draw the Court's attention to one particular point real quickly before I lose it, and that was -- and it's in our reply brief, and that is -- it's on Page 5 of our reply brief, and it's 21 CFR Section 314.94 (a) (12) (viii), and it reads:

"Once an amendment is submitted, the ANDA application will no longer be considered to contain the prior certification."

That is the rule. That's the FDA rule. And the evidence and the documents and everything in front of you, Your Honor, reveals very clearly -- and Caraco does not dispute this. They can't. The FDA asked Caraco for a new certification in August of 2009 and they have never recertified, and the rule that applies is the rule I read you that once they made that amendment, the amendment to the Section viii, once they submitted it, the ANDA application will no longer be considered to contain the prior certification,

[*29]

which is what Mr. Klein has argued to you, that he has this prior Paragraph IV that somehow got revived.

MR. KLEIN: Well, Mr. Sitzman's admitting a few material undisputed facts, which is that the original Paragraph IV certification was in the amendment as well and then the FDA asked us to change the certification, and once the Federal Circuit vacated the injunction, we clarified to the FDA that we were no longer maintaining the Section viii statement, which left the same Paragraph IV certification, the exact same Paragraph IV certification that has been in every single amendment throughout this entire litigation, and that is undisputed, Your Honor.

THE COURT: All right. Here is what I want. I want a statement of material facts from Caraco, material facts in separately numbered paragraphs in nonargumentative form establishing that there is jurisdiction based upon its filings, et cetera. You understand that. At that point if Novo wants discovery

of documents with the FDA Caraco will have to respond. If there are documents with the FDA that Caraco does not want to produce for whatever reason -- first of all, it can have a confidentiality order as to anything it produced, but if there are documents, it knows how to deal with that response to that notice for production of documents, and then we may end up having to get a Vaughan index, I don't know. But you folks have a factual dispute as to exactly what occurred, and that's

[*30]

going to require a statement of material facts justifying the jurisdiction together with an appendix of the documents with the appropriate paragraphs, et cetera, language highlighted.

I have to conclude this now because I have another commitment, but if you feel that you want to further discuss it before we finalize the action, you let Julie know and we'll have another call tomorrow or sometime this week to clarify. But as this comes across to me, and I'm not, I didn't -- I have read your briefs once and I have looked at the exhibits once, but I was unable to get my arms around them and that's why I asked this series of questions, and it appears to me that my series of questions to you when we started brought to the surface this factual dispute in a way that's not presented well by the existing set of papers on the motion to dismiss for lack of jurisdictions. Okay? And I really have to stop at this point, but if you think that further discussion is in order, you let Julie know once you get this transcript and we will continue this dialog, so to speak, before we conclude as to what must be done to deal with this motion to dismiss for lack of jurisdiction.

MR. SITZMAN: Your Honor, and I have to let you go, but there is a very important issue that we have to deal with and, as you know, I want to deal with this right away. Can we defer the briefing on any of the other pending motions and anything else until --

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THE COURT: Well, what other pending motions are there?

MR. SITZMAN: Well, we have a pending motion -- Caraco has renewed its motion for summary judgment of patent misuse.

THE COURT: When did it do that?

MR. SITZMAN: It did that when it submitted those post-trial briefs on September 7th.

THE COURT: No, I don't recall that.

MR. SITZMAN: Well, they lodged that along with their post-trial briefs. Again, the patent misuse was not part of the trial and is not part of any issue --

THE COURT: I don't know what briefs you are talking about. I will have to look them up. I can't even begin to answer. I don't want to delay anything at this point. You can send me an email as to this point and tell me what to look at, but I don't have any recollection -- Julie has not put on my desk any post-trial briefs. The only thing she has put on my desk is a list of the exhibits, a list of the witnesses, and a huge book of exhibits, a gigantic three-ring binder. That's the only thing I have seen.

MR. SITZMAN: All right. Your Honor, we will prepare an email to you on this because I do think

this jurisdictional issue, as you know, has got to be sorted out --

THE COURT: Well, I know it has to be sorted out, but

[*32]

I don't want to delay the briefing on -- the post-trial briefing on the trial.

MR. SITZMAN: Okay, understood, but I will send you an email on this patent misuse, which really does not have a place --

THE COURT: I lost them. Let them call back. I've got to go. You can talk to them. Tell Julie to call them back. I inadvertently cut them off.

(Telephonic proceedings concluded at 3:25 p.m.)

* * * *

[Certification Omitted]

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN

NOVO NORDISK A/S and NOVO NORDISK INC.,
Plaintiffs-Counterclaim Defendants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Counterclaim Plaintiffs.

Civil Action No.: 4:05 CV 40188
Hon. Avern Cohn

DEFENDANTS' STATEMENT OF UNDISPUTED FACTS CONCERNING SUBJECT MATTER JURISDICTION

Pursuant to the telephonic hearing on September 13, 2010, as well as the Court's order on September 16, 2010, Caraco submits its "statement of the material facts relating to its ANDA, in separately numbered paragraphs, from the date filed to today, which establish jurisdiction in the Court to adjudicate the validity of the '358 patent." Dkt. No. 503 (9/16/10 Order at 5).

INTRODUCTION

Congress created an "artificial" act of infringement where, as here, "the purpose of [the ANDA] submission is to obtain approval under [the Hatch-Waxman] Act to engage in the commercial manufacture, use, or sale of a drug ... claimed in a patent or the use of which is claimed in a patent before the expiration of

such patent." 35 U.S.C. § 271(e)(2)(A). Throughout this case, Caraco has sought approval under the Hatch-Waxman Act to market generic repaglinide before the '358 patent expires, and Novo has claimed that such action will infringe. Nothing more is required to support jurisdiction. *See Bristol-Myers Squibb Co.* v. *Royce Labs., Inc.*, 69 F.3d 1130, 1130 (Fed. Cir. 1995) ("once it is clear that a party seeking approval of an ANDA wants to market a patented drug prior to the expiration of the patent, the patent owner can seek to prevent approval of the ANDA by bringing a patent infringement suit").

Novo nonetheless challenges jurisdiction on technical grounds, focusing on whether Caraco's ANDA currently contains a Paragraph IV certification for an asserted patent claim. As explained in Caraco's opposition brief, Novo has not properly construed the standards for jurisdiction under § 271(e)(2)(A) and the Declaratory Judgment Act. A Paragraph IV certification is absolutely not necessary for jurisdiction. All that matters under the plain words of the statute is whether Caraco filed an ANDA seeking approval before patent expiry, which is certainly true here. Nevertheless, the undisputed record demonstrates that Caraco has always maintained a Paragraph IV certification.

STATEMENT OF UNDISPUTED FACTS SUPPORTING JURISDICTION

Caraco has subdivided the undisputed facts concerning jurisdiction into four separate phases to simplify the jurisdictional analysis.

I. PHASE 1: INCEPTION OF CASE TO APRIL 2, 2008

(Jurisdiction is Undisputed.)

1. In 2005, Caraco filed an Abbreviated New Drug Application seeking U.S. Food and Drug Administration approval to sell generic repaglinide. This ANDA contained a "Paragraph IV" patent certification for U.S. Patent No. 6,677,358 saying:

> Caraco Pharmaceuticals Laboratories Ltd. hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 6,677,358, which as per the expiration date listed in the Orange Book for this patent will expire on June 12, 2018, ***is invalid or will not*** be infringed by the manufacture, use or sale of Caraco's **Repaglinide Tablets, U.S. Patent No., 0.5 mg, 1 mg and 2 mg** for which this application is submitted.

Ex. 1 at 11; *see also* Ex. 2 at 1 (FDA acknowledgment of Paragraph IV certification); Ex. 3 at 2 (service of Paragraph IV notice on Novo).

2. In response to Caraco's ANDA, Novo sued Caraco in June 2005 for infringement of *two* patent claims – claims 4 *and 5* of the '358 patent. Ex. 4 (Dkt. No. 1 ¶¶ 1, 12) ("Caraco has infringed the '358 patent under Title 35, United States Code, § 271(e)(2)(A) by filing the ANDA") (pertinent pages); *see also* Ex. 5 (Dkt. No. 23 ¶¶ 1, 17) (pertinent pages).

3. On August 10, 2007, FDA tentatively approved Caraco's ANDA, noting that it "contains a paragraph IV certification ... stating that the patent is invalid, unenforceable, or will not be infringed." Ex. 6 at 2-3. The tentatively approved label referenced the pa-

tented metformin-repaglinide combination. *See* Ex. 7.

4. Novo has never disputed this Court's jurisdiction from the outset of this case until April 2, 2008.

II. PHASE 2: APRIL 2, 2008, TO OCTOBER 2, 2009

(Caraco's ANDA Contained a Paragraph IV for at Least One Asserted Claim, i.e., Claim 5.)

5. On April 2, 2008, Caraco submitted a "Telephone Fax Labeling Amendment" that included proposed revisions to Caraco's patent certifications under the heading "*SUGGESTED STATEMENTS OF CERTIFICATION* UNDER SECTION 505(j)(2)(A)(vii) AND 21 CFR 314.94(a)(12)." Ex. 8 at C0172247 (emphasis added). This "suggested" statement included a Paragraph IV certification materially identical to the original Paragraph IV certification in effect at the time of tentative FDA approval:

> **CARACO PHARMACEUTICAL LABS LTD.** hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. **6,677,358**, which as per the expiration date listed in the Orange Book for this patent will expire on June 12, 2018, ***is invalid, unenforceable or will not be infringed*** by the manufacture, use or sale of **Caraco's Repaglinide Tablets, U.S. Patent No., 0.5 mg, 1 mg and 2 mg** for which this application is submitted.

Id. at C0172248.

6. Caraco's suggested certification *separately* included the following section viii statement *in addition to the Paragraph IV certification*:

> **CARACO PHARMACEUTICAL LABS LTD.** hereby certifies that with reference to U.S. Patent No. 6,677,358 (which expires on June 12, 2018, as per the Orange Book) and to the extent that it is a method-of-use patent, Caraco (the applicant) does not seek approval for use of Repaglinide in combination with Metformin to lower blood glucose (as specified under U-546 listed against U.S. Patent No. 6,677,358).

Id. at C0172250. In support, Caraco proposed a generic repaglinide label that would have "carved out" information about the patented metformin-repaglinide combination. *Id.* at C0172259, C0172265-66, C0172268, C0172274, C0172276-77, C0172279-80.[1]

7. In July 2008, Novo moved to dismiss its case for lack of jurisdiction. Dkt. No. 92. Novo voluntarily

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[1] Caraco moved for summary judgment of non-infringement based on its suggested section viii statement and proposed "carved-out" label. Dkt. No. 185. Novo opposed that motion, arguing that "the Court should deny Defendants' motion as unripe, or at a minimum, stay consideration until the FDA takes action upon which summary judgment may be based." Ex. 9 (Dkt. No. 278 at 8); *see also* Ex. 10 (Dkt. No. 279 at ¶ 8) (asserting that Caraco's proposed section viii amendment was "irrelevant" because "the only label for generic repaglinide that has received any kind of FDA approval is a label that Caraco submitted on April 13, 2007, that includes information on the metformin-repaglinide combination therapy claimed by the '358 patent") (pertinent pages); Ex. 11 (Dkt. No. 205 at 15) (same). The Court never ruled on Caraco's motion for summary judgment of non-infringement.

withdrew its motion in August 2008 (Dkt. No. 107), less than a month before the Court was to hold a hearing (*see* Dkt. No. 103). Thereafter, Novo continued to actively litigate the case, taking and defending multiple depositions and filing numerous pleadings.

8. In May 2009, Novo changed its "use code" description for the '358 patent from "U-546—Use of repaglinide in combination with metformin" to "U-968—A method for improving glycemic control in adults with type 2 diabetes mellitus." Ex. 12 at NOVO-6901135, NOVO-6901138.

9. On June 11, 2009, Caraco filed its Third Amended Answer and Counterclaim. It included a new counterclaim and defense seeking relief because Novo's use code change was preventing FDA from approving Caraco's suggested section viii statement and non-infringing label. It also maintained Caraco's affirmative defenses and counterclaims challenging patent validity and enforceability. Ex. 13 (Dkt. No. 309) (pertinent pages).

10. On August 3, 2009, FDA sent Caraco a "labeling deficiencies" letter instructing Caraco to "submit an updated patent certification addressing the 6,677,358 patent and its associated Use Code, U-968." Ex. 14 at C0209149. FDA directed Caraco to "[r]evise [its] labeling" to "[a]dd back" information about the patented metformin-repaglinide combination. *Id.*; *see also* Ex. 22 at 3 ("In light of the change in the factual circumstance regarding the use code for the '358 patent, [Novo's Petition for Reconsideration] and Petition for Stay [of FDA's December 2008 citizen petition ruling allowing the section viii statement] are denied as moot").

11. On September 2, 2009, Novo filed a Reply and Affirmative Defenses to Caraco's Third Amended Counterclaim, its last pleading in this case. Ex. 15 (Dkt. No. 372) (pertinent pages). In that pleading, Novo stated:

a. "Novo Nordisk ... admits that the proposed label Caraco submitted to the Food & Drug Administration ('FDA') in April 2008 did not include information regarding repaglinide-metformin combination therapy, *but avers that the FDA has subsequently directed Caraco to include in its label information regarding repaglinide-metformin combination therapy*." *Id.* ¶ 38 (emphasis added).

b. "Novo Nordisk admits that there is an actual controversy over the infringement of the '358 patent, but that Caraco and Sun have stipulated to infringement of the '358 patent under certain labeling." *Id.* ¶ 80.

c. Novo admitted that the Court has jurisdiction over Caraco's counterclaims for declaratory judgment of non-infringement, patent invalidity, and inequitable conduct. *Compare* Ex. 13 (Dkt. No. 309 ¶ 75) *with* Ex. 15 (Dkt. No. 372 ¶ 75).

12. On September 25, 2009, this Court entered an injunction based on Caraco's new counterclaim that would have required Novo to restore its original use code description. Dkt. No. 423.

13. On October 2, 2009, the parties filed a stipulation "to streamline the pending ANDA litigation." It states in relevant part:

a. "Novo Nordisk is presently asserting claims 4 and 5 of the '358 patent in [this] litigation."

b. "Novo Nordisk agrees not to pursue any claim for infringement by Caraco of claim 5 of the '358 patent in the pending ANDA litigation."

c. "Caraco agrees not to pursue any claim for invalidity of claim 5 of the '358 patent in the captioned ANDA litigation."

d. "Notwithstanding the foregoing, Caraco is maintaining its Paragraph IV certification with the FDA as to claims 1-3 and 5 of the '358 patent in its pending ANDA[.]"

Ex. 16 (Dkt. No. 438).

14. Caraco's ANDA thus maintained a Paragraph IV certification as to at least one asserted claim (*i.e.*, claim 5) from the outset of this litigation until October 2, 2009. *Id.*

III. PHASE 3: OCTOBER 2, 2009, TO MAY 26, 2010

(FDA Required Caraco to Abandon its Section viii Statement and Seek Approval for the Patented Use.)

15. As of October 2, 2009 – indeed, since August 3, 2009 – FDA has directed Caraco to abandon its section viii statement and submit a proposed label that would infringe the patent. As Novo explained, FDA instructed Caraco in August to "'submit an updated patent certification [*i.e.*, Paragraph IV certification without any section viii statement] addressing the ['358] patent and its associated use code' and to '[r]evise [its] labeling' to include information on repaglinide-metformin combination therapy" covered by claim 4 of the '358 patent. Ex. 17 (Dkt. No. 478: Novo Mot. to Dismiss at 4) (pertinent pages); *see also* Ex.

23 at 3 (Dkt. No. 491: stipulation that such a label would infringe).

16. The district court action was stayed on October 16, 2009, pending an appeal of the Court's September 25 injunction. *See* Ex. 18 (Dkt. No. 454). This stay was pursuant to a stipulation by the parties that contemplated a trial on patent validity, without "delay," if the Federal Circuit vacated the injunction. *Id.* The use code injunction also was stayed pending appeal. Order Staying Injunction, *Novo Nordisk* v. *Caraco Pharmaceutical Labs.*, Fed. Cir. Case No. 2010-1001 (Oct. 27, 2009).

17. On April 14, 2010, the Federal Circuit issued a decision vacating this Court's injunction. *See Novo Nordisk A/S* v. *Caraco Pharm. Labs., Ltd.*, 601 F.3d 1359 (Fed. Cir.), *reh'g denied*, 615 F.3d 1374 (2010).

18. The Federal Circuit's ruling foreclosed Caraco's ability to proceed with its suggested section viii statement, which was and remains blocked by Novo's new use code. *See id.* (JJ. Dyk and Gajarsa, dissenting); *see also* Ex. 14 at C0209149.

IV. PHASE 4: MAY 26, 2010, TO PRESENT

(Caraco's ANDA Presently Contains a Paragraph IV Certification for all Claims and Seeks Approval for the Patented Use.)

19. On May 26, 2010 – *before* trial in this case began – Caraco responded to FDA's August 3, 2009, instruction to "submit an updated patent certification addressing the 6,677,358 patent and its associated Use Code, U-968." Ex. 14 at C0209149; Ex. 19 at 1. Consistent with the regulations, Caraco opted to send FDA a letter in lieu of a formal ANDA amendment "to clarify the status of Caraco's patent certification

in light of [the Federal Circuit's] decision." Ex. 19 at 1; *see also* 21 C.F.R. § 314.94(a)(12)(viii) ("An applicant shall submit an amended certification *by letter or as an amendment to a pending application* or by letter to an approved application. Once an amendment or letter is submitted, the application will no longer be considered to contain the prior certification") (emphasis added).

20. After recapping the pertinent regulatory history, Caraco explained to FDA that it has been forced to "maintain its paragraph IV certification as to *all claims* of the '358 patent," *i.e.*, the "paragraph IV certification as of the time of tentative approval":

> it is Caraco's understanding that FDA has currently decided to reject the proposed section viii statement with regard to claim 4 of the '358 patent and, therefore, that FDA is now deeming Caraco's ANDA to contain a paragraph IV certification as of the time of tentative approval. Caraco appreciates that, depending on the resolution of the appeals process relating to the section viii issue, *Caraco may ultimately need to maintain its paragraph IV certification as to all claims of the '358 patent to obtain final approval. However, it is currently maintaining that certification under protest.*

Id. at 2-3 (emphasis added).

21. Through this "amended certification by letter," Caraco abandoned its suggested section viii statement. 21 C.F.R. § 314.94(a)(12)(viii) ("Once an amendment or letter is submitted, the application will no longer be considered to contain the prior certification."). But it reserved the right to "amend its pa-

tent certification to again make a section viii statement as to claim 4 and carve the patented use out of its label" if circumstances changed. Ex. 19 at 3.

22. Caraco's current ANDA proposes a label (submitted September 20, 2010) that includes information on the metformin-repaglinide combination therapy claimed by the '358 patent. Ex. 20 at C0209354-55, C0209363, C0209365.

V. CONCLUSION

23. At all times since Caraco first sought FDA approval to sell generic repaglinide, its ANDA contained a Paragraph IV certification that said either this:

> Caraco Pharmaceuticals Laboratories Ltd. Hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 6,677,358, which as per the expiration date listed in the Orange Book for this patent will expire on June 12, 2018, ***is invalid or will not*** be infringed by the manufacture, use or sale of Caraco's **Repaglinide Tablets, U.S. Patent No., 0.5 mg, 1 mg and 2 mg** for which this application is submitted.

or this:

> **CARACO PHARMACEUTICAL LABS LTD**. hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. **6,677,358**, which as per the expiration date listed in the Orange Book for this patent will expire on June 12, 2018, ***is invalid, unenforceable or will not be infringed*** by the manufacture, use or sale of **Caraco's Repaglinide Tablets, U.S. Patent No., 0.5 mg, 1**

> **mg and 2 mg** for which this application is submitted.

Exs. 1 at 2000025, 8 at C0172248; *see also Novo Nordisk* v. *Caraco*, 601 F.3d 1359, 1363 (Fed. Cir. 2010) (In April 2008, "Caraco submitted an amended ANDA *with a Paragraph IV certification for the '358 patent* and a section viii statement declaring that Caraco was not seeking approval for the repaglinide-metformin combination therapy") (emphasis added).

24. At all times since Caraco first sought FDA approval to sell generic repaglinide, it was seeking FDA approval to market generic repaglinide before the '358 patent expired. *See* Ex. 1 at C0000025; Ex. 8 at C0172248; Ex. 19 at C0209292.

25. FDA never approved Caraco's suggested section viii statement or carved-out label. *See* Ex. 14 at C0209149. On the contrary, "the only label for generic repaglinide that has received any kind of FDA approval is a label that Caraco submitted on April 13, 2007, that includes information on the metformin-repaglinide combination therapy claimed by the '358 patent." Ex. 10 (Dkt. No. 279 at ¶ 8); *see also* Ex. 9 at 7; Ex. 11 at 6, 15.

26. Novo alleges, and has consistently alleged throughout this litigation, that Caraco's marketing of generic repaglinide before expiration of the '358 patent will infringe claim 4 of that patent. *See* Ex. 9 at 16-17.

27. On June 8, 2010, during trial in this case, counsel for Novo represented to the Court that "[t]here is no challenge to jurisdiction." Ex. 21 at 88.

* * * *

[Signature Blocks and Certificate of Service Omitted]

September 30, 2010

PETITIONER'S BRIEF

No. 10-844

In the Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD. AND SUN PHARMACEUTICAL INDUSTRIES, LTD., PETITIONERS

v.

NOVO NORDISK A/S AND NOVO NORDISK, INC., RESPONDENTS

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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QUESTION PRESENTED

Drugs approved by the Food & Drug Administration (FDA) often have multiple uses, some patented and some unpatented. In that situation, the Hatch-Waxman Act allows generic drug makers to market a drug for specific uses not claimed by any patent. But FDA lacks the expertise needed to determine whether particular uses are patented, so it defers to brand-name drug companies' descriptions of the scope of their patents. Thus, a brand-name company can block FDA's approval of a generic drug by submitting overbroad descriptions of its patent to the agency, such that a patent covering one use of the drug is effectively expanded to cover non-infringing uses.

To combat this problem, the Act authorizes courts to order brands to "correct" the "patent information" they submitted to FDA. If a brand files "an action for patent infringement" based on a patent covering "a use" of a drug, the Act permits the generic company to file a "counterclaim seeking an order requiring the [patent] holder to correct or delete the patent information submitted by the holder * * * on the ground that the patent does not claim * * * an approved method of using the drug." 21 U.S.C. § 355(j)(5)(C)(ii)(I). The Federal Circuit held that the counterclaim provision authorizes "delet[ing]" improperly listed patents but not "correct[ing]" information that misrepresents the scope of the patent. The question presented is:

> Whether the Hatch-Waxman Act counterclaim provision (21 U.S.C. § 355(j)(5)(C)(ii)(I)) applies where (1) there is "an approved method of using the drug" that "the patent does not claim," and (2) the brand submits "patent information" to FDA that misstates the patent's scope, requiring "correct[ion]."

PARTIES TO THE PROCEEDINGS

Petitioners' original Rule 29.6 Statement, as amended on June 15, 2011, and supplemented by Respondents' Rule 29.6 Statement in the brief in opposition, remains accurate.

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GLOSSARY OF ABBREVIATIONS

Act	Hatch-Waxman Act
ANDA	Abbreviated New Drug Application
Counterclaim	21 U.S.C. § 355(j)(5)(C)(ii)(I)
FDA	Food & Drug Administration
NDA	New Drug Application
Orange Book	FDA Orange Book: Approved Products With Therapeutic Equivalence Evaluations
Paragraph IV	21 U.S.C. § 355(j)(2)(A)(vii)(IV)
Section viii	21 U.S.C. § 355(j)(2)(A)(viii)

INTRODUCTION

The Hatch-Waxman Act[1] provides a path to expedited FDA approval of generic drugs when a drug has multiple FDA-approved uses and a brand-name drug manufacturer's patent claims at least one, but not all, of the approved uses. That path, set forth in "Section viii" of the Act, allows generic drug manufacturers to submit a "carved-out" product label that omits reference to potentially infringing uses. Pet. 6a.

Petitioners ("Caraco") here sought FDA approval to sell generic repaglinide—a diabetes drug manufactured by respondents ("Novo")—for two uses that Novo concedes do not infringe its patent. Nevertheless, to block approval, Novo told FDA that its patent *does* cover those non-infringing uses. As the district court held, Novo "seriously misrepresent[ed]" the patent's scope. Pet. 70a. But FDA—which lacks the authority and expertise to construe patents—deferred to Novo's overbroad description of its patent. FDA thus rejected Caraco's carved-out label, thereby barring Caraco from marketing generic drugs for uses that all agree are non-infringing.

The question presented boils down to whether the Act remedies such gamesmanship. It does. It authorizes counterclaims to "correct or delete the patent information submitted by the [patent] holder" whenever there is "an approved method of using the drug"

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[1] The "Hatch-Waxman Act" refers to the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984), as amended by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003).

that "the patent does not claim." 21 U.S.C. § 355(j)(5)(C)(ii)(I).

Contrary to the Act's text, structure, history, purpose, and interpretation by FDA, however, the court below held that Caraco has no remedy. Over a forceful dissent, the majority held that the counterclaim is unavailable because: (1) Novo's patent claims *one* "approved method of using the drug" at issue, even though it "does not claim" two *other* "approved methods of using the drug"; and (2) the statute effectively permits only "delet[ing]" patents that should not have been listed with FDA at all, not "correct[ing]" inaccurate "patent information" that overstates the patent's scope. Pet. 12a, 15a-16a.

The court below reached this result by announcing that the phrase "an approved method of us[e]" really means "*any* approved method of us[e]." Pet. 12a. (emphasis added). But Congress intentionally used the word "an," not "any," as confirmed by the use of "any" in the very next sentence and some 34 times in neighboring provisions. Moreover, the court read the term "patent information" as limited to "an erroneous patent number or expiration date" (Pet. 15a-16a)—*i.e.*, to exclude information about what "the patent does not claim"—contrary to both the statute's text and FDA's interpretation.

The Federal Circuit's decision thus licenses brand manufacturers to craft overbroad descriptions of their patents, and thereby to "extend [their] monopol[ies] to unpatented uses." Pet. 62a (Gajarsa, J., dissenting). Using a patent to block the marketing of concededly unpatented uses would be extraordinary under any statute, but especially one designed to expedite generic competition. This ruling must be reversed.

OPINIONS BELOW

The Federal Circuit's opinion (Pet. 1a-52a) is reported at 601 F.3d 1359. The Federal Circuit's decision denying rehearing and rehearing en banc (Pet. 53a-64a) is reported at 615 F.3d 1374. The relevant decisions of the District Court for the Eastern District of Michigan (Cohn, J.) (Pet. 65a-103a) are reported at 649 F. Supp. 2d 661 and 656 F. Supp. 2d 729.

JURISDICTION

In June 2005, Novo sued Caraco for patent infringement, asserting jurisdiction under 21 U.S.C. § 355(j)(5)(C)(ii); 28 U.S.C. §§ 1331, 1338, 2201, and 2202; and 35 U.S.C. § 271(c)(2). Following the district court's injunction order in 2009 and a timely interlocutory appeal by Novo, the Federal Circuit entered judgment on April 14, 2010, and denied a timely rehearing petition on July 29, 2010. On October 18, 2010, the Chief Justice extended the time to petition for certiorari to December 23, 2010. This Court has jurisdiction under 28 U.S.C. § 1254(1), and granted certiorari on June 27, 2011.

STATUTORY AND REGULATORY PROVISIONS INVOLVED

Relevant statutory and regulatory provisions are set forth in the appendix to this brief. See App. 1a-116a (21 U.S.C. § 355); 117a-132a (21 C.F.R. § 314.53). The counterclaim provision at issue states:

> (C) Civil action to obtain patent certainty.—
>
> * * *
>
> (ii) Counterclaim to infringement action.—
>
> (I) In general.—If * * * the [NDA] holder * * * for the drug that is claimed by the patent or a use of

> which is claimed by the patent brings a patent infringement action against the [ANDA] applicant, the [ANDA] applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) of this section on the ground that the patent does not claim either—
>
> (aa) the drug for which the application was approved; or
>
> (bb) an approved method of using the drug.

21 U.S.C. § 355(j)(5)(C)(ii)(I) (App. 55a).

STATEMENT

A. The structure of the Hatch-Waxman Act

The Hatch-Waxman Act governs FDA approval of new and generic drugs. 21 U.S.C. § 355. The Act is designed to "strike a balance between two competing policy interests: (1) inducing pioneering research and development of new drugs and (2) enabling competitors to bring low-cost, generic copies of those drugs to market." *Caraco Pharm. Labs, Ltd.* v. *Forest Labs., Inc.*, 527 F.3d 1278, 1282 (Fed. Cir. 2008) (citations and brackets omitted).

To expedite FDA approval, the Act allows generic manufacturers to submit to FDA an abbreviated new drug application (ANDA) instead of a full-blown new drug application (NDA). 21 U.S.C. § 355(j)(2)(A). The timing of an ANDA's approval depends largely on the scope of the patents covering the brand-name drug and, if necessary, resolution of litigation over patent infringement. Accordingly, NDA filings must identify all non-process patents that arguably protect the new drug. *Id.* § 355(b)(1), (c)(2). FDA lists these patents in its book of "Approved Products With The-

rapeutic Equivalence Evaluations"—the "Orange Book"—which alerts generics to the scope of claimed patent rights. Pet. 4a-5a.

As detailed below, the Act provides two different ways for generic manufacturers to address patents when seeking FDA approval. One way is the "Paragraph IV" process, which facilitates the resolution of patent infringement disputes between brand-name and generic companies; the other is the "Section viii" process, which avoids such litigation when generics seek to sell drugs for uses *not* covered by the brand's patents. In both instances, "Congress sought to get generic drugs into the hands of patients at reasonable prices—fast." *In re Barr Labs., Inc.*, 930 F.2d 72, 76 (D.C. Cir. 1991).

1. Paragraph IV certifications

The Paragraph IV process applies when a generic manufacturer seeks to market a drug arguably covered by an unexpired patent listed in the Orange Book, in which case "the generic is generally required to certify that the patent * * * is invalid or will not be infringed by the sale or use of the [generic] drug." Pet. 24a. This is called a "Paragraph IV" certification. 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

The Act treats a Paragraph IV certification as an artificial act of patent infringement, permitting the brand to sue the generic. 35 U.S.C. § 271(e)(2). Alternatively, if the brand fails to sue, the generic may file its own "[c]ivil action to obtain patent certainty." 21 U.S.C. § 355(j)(5)(C)(ii)(I). In either case, if the generic prevails in court and its ANDA otherwise qualifies, FDA must approve generic marketing on the date when the district court enters judgment. *Id.* § 355(j)(5)(B)(iii)(I).

2. Section viii applications

The Act also offers an alternative path to FDA approval—a "Section viii" statement. "Section viii addresses scenarios where a patent claims at least one, but not all, approved methods of using a drug." Pet. 13a-14a. Section viii is typically invoked when the patent on a chemical compound used in a drug has expired, and the Orange Book lists a "method" patent —one covering a specific method of using the compound—that "does not claim a use for which the applicant is seeking approval." 21 U.S.C. § 355(j)(2)(A)(viii) (App. 36a).

Normally, a generic drug label must be identical to that of the brand. *Id.* § 355(j)(2)(A)(v), (j)(4)(G); 21 C.F.R. § 314.94(a)(8)(iv). Section viii, however, allows a generic to "submit a proposed label to the FDA that does not contain [*i.e.*, carves out] the patented method of using the listed drug." Pet. 5a. By obtaining approval to "delet[e] patented use[s] from its proposed label," generics "avoid infringement." Pet. 60a.

Importantly, however, when deciding whether to approve a carved-out label, FDA relies on the brand's description of the scope of its patent. Pet. 6a; 21 C.F.R. § 314.53(f). FDA will not review the patent itself, because the agency lacks both the institutional "expertise in patent matters" and a "statutory basis" to interpret patents. *Applications for FDA Approval to Market a New Drug*, 68 Fed. Reg. 36676, 36683 (June 18, 2003) ("2003 Final Rule"). "[FDA's] role in listing patents in the Orange Book is 'ministerial'; it simply lists the patent information that it receives from brand manufacturers, expecting those parties to properly abide by the statutory and regulatory mandates." Pet. 60a-61a n.4.

To enable FDA to review proposed carved-out labels, the patent information that brands submit to FDA includes what is known as a "use code narrative" (Pet. 4a) or simply a "patent use code" (JA500). "FDA approves the section viii statement only where there is no overlap between the proposed carve-out label * * * and the [brand's] use code." Pet. 6a. Unless the agency can confirm that the generic's carved-out labeling avoids the brand's use code, it will require that labeling to be identical to the brand's. 21 U.S.C. § 355(j)(2)(A)(v), (j)(4)(G); 21 C.F.R. § 314.94(a)(8)(iv). Thus, accurate use codes are "essential to the [Act's] operation." Pet. 29a.

B. The Act's counterclaim provision

Aware of brands' efforts to "block generic competition by making unwarranted claims to patent coverage" (Pet. 25a), Congress enabled generics "in a Paragraph IV suit to assert a counterclaim challenging the accuracy of the 'patent information' submitted to the FDA" (Pet. 6a). As Congress provided:

> (I) In general.—If * * * the [NDA] holder * * * for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the [ANDA] applicant, the [ANDA] applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) of this section on the ground that the patent does not claim either—
>
> > (aa) the drug for which the application was approved; or
> >
> > (bb) an approved method of using the drug.

21 U.S.C. § 355(j)(5)(C)(ii)(I) (App. 55a).

This provision was not always part of the Act; and in 2001 the Federal Circuit ruled in *Mylan Pharmaceuticals, Inc.* v. *Thompson*, 268 F.3d 1323, that the Act did not authorize private actions to correct inaccurate patent listings. The generic there (Mylan) had filed a Section viii statement indicating that a listed patent did not claim a use for which Mylan sought approval. When FDA asked for clarification of the patent's scope, the brand responded that its patent *did* claim that use, prompting rejection of Mylan's Section viii statement. Mylan then sued, seeking an injunction requiring the brand to delist the patent. *Id.* at 1328. Describing Mylan's claim as "analogous to those barred in [a] long line of cases precluding private rights of action," the court rejected it. *Id.* at 1332.

Shortly thereafter, the Federal Trade Commission (FTC) published a lengthy study describing strategies that brands used to delay generic entry—including "improper Orange Book listings." FTC, *Generic Drug Entry Prior to Patent Expiration: An FTC Study*, v (July 2002). FTC "subpoenaed documents and information from brand-name and generic drug manufacturers, and examined instances since 1992 in which generic applicants filed an application with FDA seeking to enter the market with a generic version of a drug product prior to expiration of the brand-name drug products' patents." *Id.* at ii. Noting that generics lacked any means of challenging brands' patent information in court, FTC proposed that Congress permit generics to bring a counterclaim in patent infringement suits. *Ibid.* Additionally, FTC stated that "it appears useful for the FDA to clarify its listing requirements." *Ibid.*

C. FDA's regulations

FDA acted first, amending its regulations in June 2003 to clarify the "need for accurate and detailed information related to the approved methods of use claimed in [listed] patent[s]." 68 Fed. Reg. at 36682. These "Submission of patent information" regulations contain special rules for method patents that claim one or more approved methods of using a listed drug. Under 21 C.F.R. § 314.53, brands must submit a description of each approved method of using the drug claimed by its patent, together with other information describing the scope of the related method patent's claims:

> (P) Information on each method-of-use patent including the following:
>
> > (1) Whether the patent claims one or more approved methods of using the approved drug product and a description of each approved method of use or indication and related patent claim of the patent being submitted;
> >
> > (2) Identification of the specific section of the approved labeling for the drug product that corresponds to the method of use claimed by the patent submitted; and
> >
> > (3) *The description of the patented method of use as required for publication.*

Id. § 314.53(c)(2)(ii)(P) (emphasis added) (App. 127a).

Brands must submit this patent description on FDA Form 3542 (*id.* § 314.53(c)(1)), which confirms that use codes must track the method patent's scope:

> The use code designates a method of use patent that claims the approved indication or use of a

> drug product. *Each approved use claimed by the patent should be separately identified in this section* and contain adequate information to assist * * * ANDA applicants in determining whether a listed method of use patent claims a use for which the * * * ANDA applicant is not seeking approval.

Pet. 214a (emphasis added); 68 Fed. Reg. at 36682-36683. Further, FDA requires brands to verify their patent information under penalty of perjury, cautioning that knowingly filing false information violates 18 U.S.C. § 1001. *Id.* at 36686.

Just months after FDA enacted these regulations on the "Submission of patent information," Congress undertook to "close loopholes in the law and end the abusive practices in the pharmaceutical industry * * * which have cost consumer billions," by allowing generics sued for infringement "to file a counterclaim to have the brand drug company * * * correct the patent information in FDA's Orange Book." 149 Cong. Rec. 31200 (2003) (Sen. Schumer).

Congress acted "with full awareness of the agency's interpretation of ['patent information']." Pet. 37a. Indeed, FDA's chief counsel twice testified concerning those regulations.[2] And as Senator Schumer, a leading sponsor, stated: "The bill provides a critical complement to the work the FDA has done in clarify-

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[2] *Legislative and Regulatory Responses to the FTC Study on Barriers to Entry in the Pharmaceutical Marketplace: Hrg. Before S. Comm. on Judiciary*, 108th Cong. 5-10 (June 17, 2003); *Examining the Senate and House Versions of the "Greater Access to Affordable Pharmaceuticals Act": Hrg. Before S. Comm. on Judiciary*, 108th Cong. 7-10 (Aug. 1, 2003) (each containing statements of D. Troy, Chief Counsel for FDA).

ing its regulations on patent listing, but it goes much further." *Legislative and Regulatory Responses to the FTC Study on Barriers to Entry in the Pharmaceutical Marketplace: Hrg. Before S. Comm. on Judiciary*, 108th Cong. 19 (June 17, 2003) ("*Legislative and Regulatory Responses Hearing*"); accord 149 Cong. Rec. at 16689 (Sen. Hatch); *id.* at 15521 (Sen. Frist). Thus, in late 2003—just six months after FDA published its final rule—Congress enacted the counterclaim provision quoted above, employing the term "patent information" defined in the regulations and Form 3542.

D. Novo's New Drug Application and Caraco's Abbreviated New Drug Application

Novo holds an NDA for repaglinide, a diabetes drug sold as PRANDIN. Novo's patent on the repaglinide compound expired in 2009. Pet. 7a.

In February 2005, Caraco became the first ANDA applicant seeking to sell generic repaglinide. Pet. 8a. Because Caraco filed a Paragraph IV certification, its proposed labeling had to list all FDA-approved uses of repaglinide. *Supra* at 6. In June 2005, Novo sued Caraco for patent infringement.

The asserted patent (the '358 patent), which expires in 2018, claims the use of "repaglinide in combination with metformin," another diabetes drug, to treat patients with type 2 diabetes. *Ibid.* This is one of three FDA-approved uses of repaglinide; the others are repaglinide by itself (monotherapy); and repaglinide combined with thiazolidinediones (TZDs). Pet. 7a. "Novo does not own patents claiming the other two approved methods of using repaglinide." Pet. 8a.

Until 2009, Novo's patent use code correctly described its patent as covering *only* "use of repaglinide

in combination with metformin to lower blood glucose." Pet. 44a-45a.

E. Novo's revised patent use code and FDA's ruling on Caraco's Section viii application

At FDA's suggestion, when Novo's patent on the repaglinine *compound* was nearing expiration, Caraco invoked Section viii, "declaring that Caraco was not seeking approval for the repaglinide-metformin combination therapy" and asking to carve out of the labeling any reference to that combination. Pet. 8a; JA166-176. Based on Novo's original use code, and the lack of any overlap between that use code and Caraco's proposed labeling, FDA ruled that Section viii approval would be proper. Pet. 8a.

But in "'response to th[is] section viii ruling,'" Novo broadened its use code to read: "a method for improving glycemic control in adults with type 2 diabetes mellitus." Pet. 49a, see *id.* at 45a. Based on this broadened description of Novo's patent, FDA "reversed itself and rejected Caraco's proposed labeling carve-out"—requiring Caraco to include the patented repaglinide-metformin combination in its labeling. Pet. 46a. Thus, by misrepresenting the scope of its patent, Novo concocted a claim that Caraco's labeling would infringe—effectively expanding the scope of Novo's patent to cover *unpatented uses* until it expired in 2018. Further, by so broadly describing its patent on combination therapy, Novo effectively extended the term of its patent on the repaglinide *compound*, which expired in 2009, until 2018.

Caraco thus filed a counterclaim, seeking partial summary judgment and an injunction. Finding that Novo's patent use code "seriously misrepresents the approved method of use covered by [the '358 patent],"

the district court enjoined Novo to restore its original use code. Pet. 70a. Novo's new use code is "so broad as to incorrectly suggest that the '358 patent generically covers three (3) different FDA-approved methods of use of repaglinide," the court explained, when in fact "the first two (2) uses are not covered." Pet. 68a.[3]

F. The Federal Circuit's divided ruling

In a ruling that spawned three opinions, a divided Federal Circuit panel (Rader, Clevenger, Dyk, JJ.) reversed.

First, reading the phrase "*an* approved method of use" to mean "*any* approved method of use," the majority (per Rader, J.) reasoned that a counterclaim is available "only if the listed patent does not claim *any* approved methods of using the listed drug." Pet. 12a (emphasis added). Although the word "any" appears elsewhere in the same provision (§ 355(j)(5)(C)(ii)(II)), the court never discussed this language, finding "no ambiguity in the statut[e]." Pet. 12a. Nor did the majority reconcile its ruling—which effectively limits the statute's remedy to the "delet[ion]" of patents improperly listed in the Orange Book—with the statutory language permitting the "correct[ion]" of inaccurate "patent information." Pet. 15a-16a.

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[3] The parties agreed to postpone trial on issues of patent validity and enforceability pending resolution of the appeal process. After the ruling below, the parties tried those issues in the district court, which held that the '358 patent was both invalid and unenforceable. Opp. 46a-102a. Pursuant to the parties' agreement, Novo's appeal of those issues has been stayed pending this Court's decision. See Dkt. 31, No. 2011-1223 (Fed. Cir. July 27, 2011) (stay order).

Second, the majority held that the term "patent information" is limited to "an erroneous patent number or expiration date" and "does not extend to the use code narrative." Pet. 15a-16a. Although Hatch-Waxman does not define "patent information" (see 21 U.S.C. § 321), the majority asserted that the Act had an "express statutory definition" that precluded reading the term to include use codes. Pet. 15a-17a. And although FDA's regulation, which "preceded the 2003 Amendment," "appeared to include the use code narrative under the broader heading of 'patent information,'" the court dismissed this fact as an "'opaque timing observation.'" Pet. 16a (citation omitted).

Judge Rader's opinion "recognize[d] that a broad use code covering all uses of a pharmaceutical could" preclude use of Section viii. Pet. 13a-14a. In his view, a generic could use "a Paragraph IV lawsuit" to prove that its "use will not overlap with * * * the patented use." *Ibid.* But that was incorrect, because a generic generally cannot avoid infringement without the benefit of Section viii carved-out labeling.

Judge Clevenger, who concurred, was "not as certain" that "Paragraph IV litigation will cleanly resolve the dispute." Pet. 19a. As he recognized, "Caraco can no longer assert that its proposed labeling does not infringe." Pet. 20a. And although he blamed FDA for purportedly creating the problem—on the mistaken understanding that "FDA's request that Novo change its labeling" required changing the *use code*—he acknowledged that the outcome "upset the [Act's] careful balance of interests." *Ibid.*

Judge Dyk dissented, explaining that "the text is clear" in light of "the overall operation of the statutory scheme." Pet. 41a. "[I]nterpreting 'an approved

method' * * * to mean 'any' approved method," he observed, is "fundamentally inconsistent with the Supreme Court's admonition * * * that '[u]ltimately, context determines meaning.'" Pet. 39a. Judge Dyk also disagreed that the counterclaim was limited to situations where the patent-in-suit should not have been listed in the Orange Book *at all*. Pet. 32a. As he recognized: "Viewing [the counterclaim] as limited to complete delisting would be inconsistent with the explicit statutory language, which provides for correction of Orange Book information" as well as "deleting" it. *Ibid.*

On the "patent information" question, Judge Dyk found the majority's reading irreconcilable with both the text and FDA's interpretation—"even if the language of the statute is ambiguous, and not (as I urge) plainly contrary to the majority's interpretation." Pet. 33a; see *id.* at 30a. Moreover, because "Congress utilized the FDA's interpretation of 'patent information' * * * with full awareness," he believed that interpretation was "binding." Pet. 37a-38a.

Judge Dyk also clarified that FDA did not cause "Caraco's predicament"—citing Novo's admission that "FDA did not require [a new use code]" and explaining that "absolutely nothing in the statute or regulations * * * required Novo to change the use code to track [its labeling]." Pet. 47a-48a. But he agreed with Judge Clevenger that generics are "left without any remedy to correct an erroneous Orange Book listing" for "a method of use patent." Pet. 51a. "Novo's adoption of a broad use code for PRANDIN likely prevents Caraco from being able to disprove infringement," he explained, "because Caraco is now compelled to include information regarding the patented combination therapy in its label." Pet. 50a. In

short, "the majority's crabbed view of the statute sanctions an unjustified manipulation of the Orange Book" and "cannot be what Congress intended." Pet. 51a.

G. The dissent from the denial of rehearing

Over a dissent by Judges Gajarsa and Dyk, the Federal Circuit denied en banc review. As Judge Gajarsa explained, "[b]oth constructions" adopted by the panel's majority—its "overly narrow construction of 'patent information' and [its] overly broad construction of 'an approved method of using the drug'"—"are irreconcilable with pre-existing FDA regulations, the text of the [Act], and Congressional intent." Pet. 59a. He found it "especially troubling" that the panel "refuses to give effect to [FDA's] interpretation" of "patent information," given "Congress's explicit approval of those regulations." Pet. 63a.

Furthermore, brands now have "every incentive to * * * draft exceedingly broad use codes"—thus "subverting Section viii carve-out statements." Pet. 62a, 60a. By "leav[ing] generic drug manufacturers without a remedy to challenge inaccurate Orange Book listings with respect to method of use patents," Judge Gajarsa explained, the majority's ruling "render[s] section viii a dead letter." Pet. 59a, 62a. And holding "that counterclaim relief is not available because the [patent-in-suit] covered at least one approved use * * * effectively allows a patent holder to extend its monopoly to unpatented uses." Pet. 62a. This "absurd result * * * contravenes the intent of Congress." Pet. 63a.

SUMMARY OF ARGUMENT

I. The Federal Circuit's decision is foreclosed by the text, structure, history, and purpose of the Hatch-

Waxman Act's carefully crafted counterclaim provision. The counterclaim is available here because Caraco established that Novo's patent "does not claim * * * an approved method of using the drug [repaglinide]." 21 U.S.C. § 355(j)(5)(C)(ii)(I). In fact, Novo's patent does not claim *two* of repaglinide's three approved uses. Yet Novo's broadened use code says otherwise. Under the counterclaim's plain terms, therefore, Caraco is entitled to "an order requiring" Novo to "correct" this inaccurate "patent information." *Ibid.* As the United States explains, Caraco "properly invoked the counterclaim provision by alleging that, contrary to the apparent implication of the amended use code that [Novo] submitted to FDA, the '358 patent does not claim the use of repaglinide as monotherapy, which is 'an approved method of using the drug.'" U.S. Invitation Br. 12-13.

I.A. In reaching a contrary conclusion, the majority below committed two fundamental errors. *First*, it rewrote the phrase "*an* approved method of us[e]" to mean "*any* approved method of us[e]"—such that the Act "authorizes a counterclaim only if the listed patent does not claim any approved methods of using the listed drug." Pet. 12a. This altered the statute's meaning. Congress used the word "an," not "any," which appears in the very next sentence, nine times in the surrounding subsection, and 34 times in the Act's ANDA provisions. Thus, there can be no question that Congress "act[ed] intentionally" in its "exclusion" of "any" from the counterclaim. See *Lopez* v. *Gonzales*, 594 U.S. 47, 55-56 (2006).

Further, "any" is an "expansive and unqualified" word (*e.g.*, *Salinas* v. *United States*, 522 U.S. 52, 57 (1997)), and distinctions between terms such as "an" and "any" are particularly critical in laws such as the

Food, Drug & Cosmetic Act (FDCA), where the Court takes extra care "neither to add nor to subtract, neither to delete nor to distort" Congress's phrasing. *Flemming* v. *Fla. Citrus Exch.*, 358 U.S. 153, 166 (1958). If anything, this is even more true under the finely tuned Hatch-Waxman Act (which amended the FDCA). As a leading sponsor of the 2003 amendments' noted: "Change an 'an' to a 'the' and you go from huge savings to huge cost." *Examining the Senate and House Versions of the "Greater Access to Affordable Pharmaceuticals Act": Hearing Before the Senate Comm. on the Judiciary*, 108th Cong. 119 (Aug. 1, 2003) ("*Greater Access Hearing*") (statement of Sen. Schumer). Yet changing an "an" is exactly what the court below did.

Other aspects of the counterclaim's text and structure confirm that reversal is warranted. Most fundamentally, the statute places the burden of proof on "the ANDA applicant"—the generic. The statute asks not whether the *brand* can show that its patent *does claim* "an approved method," but whether the *generic* can show "an approved method" that the patent "*does not* claim." Plainly, Caraco has carried that burden.

The decision below also nullifies the statute's language authorizing courts to order brands to "correct" inaccurate "patent information." When a patent claims *no* approved use, it should not be listed in the Orange Book at all, and the remedy is "deleting" it. If the counterclaim addressed only that situation, however, Congress's reference to "correct[ing]" patent information would become "inoperative or superfluous, void or insignificant." See *Corley* v. *United States*, 129 S. Ct. 1558, 1566 (2009). Thus, reading the statute to effectively eliminate the word "correct" is "in-

consistent with the explicit statutory language." Pet 32a (Dyk, J., dissenting).

I.B. *Second*, the court below erred in holding that Novo's patent use code is not "patent information submitted * * * under subsection (b) or (c)" of section 505 of the FDCA. 21 U.S.C. § 355(j)(5)(C)(ii)(I). By that court's reasoning, the term "patent information" "could only mean the patent number and expiration date," as that is the only patent information actually "described" in Section 505(b). Pet. 15a. But a use code describes the *patent's* scope, and thus is "*patent* information" within any fair reading of that term. And while several other Hatch-Waxman provisions refer to patent information "described in," "required by," or "prescribed by" the Act,[4] the counterclaim uses different language. It speaks of patent information "submitted under" Sections 505(b) and (c)—language used throughout the Act to reference patent information submitted under FDA's regulations. See also *Ardestani* v. *INS*, 502 U.S. 129, 135 (1991) (the term "under," followed by a statutory provision, refers to regulatory proceedings subject to, or governed by, that provision).

Furthermore, this reading of "patent information" is consistent with FDA's, which Congress adopted in enacting the counterclaim. Just months before Congress acted, FDA expressly invoked Sections 505(b) and (c) as the basis for its regulations governing "Submission of patent information"; and FDA Form 3542 states that all patent information "is provided in accordance with Section 505(b) and (c)." Pet. 211a. The "patent information" that FDA required included accurate and detailed use codes describing the scope

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[4] *E.g.*, 21 U.S.C. §§ 355(c)(2), 355(d)(6), 355(e)(4).

of the relevant patents. And Congress was both constructively and actually aware of this when it enacted the counterclaim. Given the similarity of phrasing between FDA's regulations and the counterclaim, it is evident that Congress was adopting FDA's definition in referring to "patent information * * * submitted under subsection (b) or (c) of section 505."

I.C. Reversal is also warranted because the Federal Circuit's readings of "an approved method" and "patent information" contravene "the structure of the 1984 Act taken as a whole." *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661, 669 (1990).

The point of the counterclaim statute is to provide a remedy for gamesmanship that delays generic competition. Yet the Federal Circuit read the statute in a manner that effectively licensed brands to block concededly non-infringing generic drugs, eliminated the statute's remedy for "correcting" patent information, and "eviscerate[d] Section viii." Pet. 62a (Gajarsa, J., dissenting). In effect, brands have been handed the ability to extend their patents to cover "unpatented uses." *Ibid.*

Given the complementary nature of the counterclaim and Section viii, it should take "strong evidence to persuade [the Court] that" Congress "create[d] an effective extension of the patent." *Eli Lilly*, 496 U.S. at 670, 673. Yet Novo cannot explain why Congress would authorize injunctions to "delete" misleading patent information when a patent claims *no* approved use, but not to "correct" misleading patent information used to block marketing for *a subset* of non-infringing uses. This is particularly true under an Act designed to expedite generic competition.

II. Because there is "an approved method of using the drug" that Novo's patent "does not claim," Caraco is entitled to an order requiring Novo to "correct" its use code. As the United States explains, "[a]n order to 'correct or delete' * * * patent information is appropriate * * * if the use code misleadingly suggests that the patent claims approved methods of use that it does not actually cover." U.S. Invitation Br. 12. That is exactly the situation here. And there is no question what a "correct" use code looks like, as Novo's original use code accurately detailed the only FDA-approved use claimed by Novo's patent. This Court need only reinstate the district court's injunction.

ARGUMENT

In interpreting Acts of Congress, this Court "begin[s]" with "the assumption that the ordinary meaning of the language chosen by Congress accurately expresses the legislative purpose." *Microsoft Corp.* v. *i4i Ltd. P'ship*, 131 S. Ct. 2238, 2245 (2011). The Court pays particular attention to Congress's phrasing choices in the FDCA, which "is a detailed and thorough piece of legislation" and is "quite specific" in "[i]ts treatment of many public health and food problems." *Flemming*, 358 U.S. at 166 (citation omitted). In reading that Act, the Court is especially "mindful of [Congress's] approach in terms of draftsmanship" and "sensitive to what Congress has written," taking extra care only "to ascertain—neither to add nor to subtract, neither to delete nor to distort." *Ibid.*

Congress drafted the counterclaim with just such precision. As a leading sponsor explained: To close "these loopholes," "the devil is in the details. * * * Change an 'an' to a 'the' and you go from huge savings to huge cost. Senator Gregg and I saw multiple

examples of this as we worked out the technical details of the bill with the FDA. * * * The bill * * * is extremely carefully crafted." *Greater Access Hearing*, *supra*, at 119 (statement of Sen. Schumer).

By changing the counterclaim's plain language, overlooking its statutory context, and contravening its structure, history, and purpose, the decision below fails to respect Congress's careful crafting, and must be reversed.

I. Under the Hatch-Waxman Act's precisely drawn text, as well as its structure, history, and purpose, Caraco is entitled to bring a counterclaim.

A. The Federal Circuit's reading of "does not claim an approved use" is textually untenable.

We begin with the specific words chosen by Congress. If a brand brings a patent infringement claim against a generic seeking FDA approval, the generic may bring a counterclaim:

> (I) In general.—If * * * the [NDA] holder * * * for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the [ANDA] applicant, the [ANDA] applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) of this section on the ground that the patent does not claim either—
>
> > (aa) the drug for which the application was approved; or
> >
> > (bb) an approved method of using the drug.

21 U.S.C. § 355(j)(5)(C)(ii)(I) (App. 55a).

Here, after being sued, Caraco filed a "counterclaim" establishing that the '358 patent "does not claim * * * an approved method of using the drug" repaglinide. In fact, Caraco showed that Novo's patent "does not claim" *either* repaglinide administered alone or repaglinide combined with TZDs—each of which is "an approved method of using the drug."

The Federal Circuit rejected this sensible reading of the counterclaim. The court did not dispute that there is "an approved method of using the drug" that "the ['358] patent does not claim." Rather, it held that "the counterclaim is available only if the * * * patent does not claim *any* approved methods," because "'*an approved method' means 'any approved method*.'" Pet. 12a, 13a (emphasis added). For several reasons, that reading is textually impermissible.

1. **Substituting "any" for "an" alters the meaning of the counterclaim, and ignores the use of "any" in the next sentence.**

Most importantly, Congress did not say "any"; it said "an." "[C]ourts must presume that a legislature says in a statute what it means and means in a statute what it says there. When the statutory language is plain, the sole function of the courts—at least where the disposition required by the text is not absurd—is to enforce it according to its terms." *Arlington Cent. Sch. Dist. Bd. of Educ.* v. *Murphy*, 548 U.S. 291, 296 (2006) (citations and quotations omitted). And the statutory language is plain here.

a. The counterclaim required Caraco to show that "the patent [in suit] does not claim * * * an approved method of using the drug." Having made that show-

ing for two approved methods—repaglinide monotherapy and repaglinide combined with TZDs—Caraco should prevail. It is irrelevant that Caraco also could have prevailed if it had been able to show that the patent did not claim *any* approved use—in that "an" is necessarily satisfied if the broader "any" is satisfied. This is the natural effect of Congress choosing "an" rather than "any."

By substituting "any" for "an," the majority below changed the statute's meaning. Unlike "an," "any" is an "expansive and unqualified" word with a "wide reach" and a "sweeping" meaning. *Salinas*, 522 U.S. at 57 ("expansive, unqualified"); *Massachusetts* v. *EPA*, 549 U.S. 497, 528 (2007) ("sweeping"); *Boyle* v. *United States*, 129 S. Ct. 2237, 2243 (2009) ("obviously broad"; "wide reach"); accord *Kasten* v. *Saint-Gobain Performance Plastics Corp.*, 131 S. Ct. 1325, 1332 (2011) ("broad interpretation"); *Repub. of Iraq* v. *Beaty*, 129 S. Ct. 2183, 2189 (2009) ("of course * * * expansive"); *Ali* v. *Fed. Bureau of Prisons*, 552 U.S. 214, 219 (2008) ("broad"); *Dep't of Housing & Urban Dev.* v. *Rucker*, 535 U.S. 125, 131 (2002) ("expansive"); *United States* v. *Gonzales*, 520 U.S. 1, 5 (1997) ("an expansive meaning, that is, one or some indiscriminately of whatever kind") (citation omitted). As these many citations show, Congress knows how to use the expansive term "any." Yet it did not do so in the counterclaim phrase at issue. Cf. *Chamber of Commerce of the United States of Am.* v. *Brown*, 554 U.S. 60, 72 (2008) (state statute; "expansive[]"); *Norfolk S. Ry. Co.* v. *Kirby*, 543 U.S. 14, 31-32 (2004) ("expansive" term in contract, lending "obvious" meaning).

That decision is all the more significant given that Congress used the term "any" in the very next sen-

tence: "Subclause (I) does not authorize the assertion of a claim described in subclause (I) in *any* civil action or proceeding other than a counterclaim described in subclause (I)." 21 U.S.C. § 355(j)(5)(C)(ii)(II) (emphasis added). Indeed, Congress used "any" nine more times in the surrounding subsection (21 U.S.C. § 355(j)(5)(C)) and 34 times in the ANDA provisions of the Hatch-Waxman Amendments (*id.* § 355(j)).

"[W]here Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion of exclusion." See *Lopez*, 594 U.S. at 55 (internal quotation marks omitted). All the more so where a term appears in the very same provision. Congress's refusal to use "any" in the phrase at issue thus confirms that "any" must not be read into that phrase. See *Sullivan* v. *Everhart*, 494 U.S. 83, 89-90 (1990) (interpreting a statute requiring HHS to correct mistaken payments of benefits to permit "netting" out multiple payments; explaining that, "[i]f Congress had in mind only * * * individual monthly payments * * * it would have been more natural to refer to 'the correct amount of *any payment*,' and to require adjustment 'with respect to *any payment*,' since the "fuller context" showed that "[t]his terminology is used elsewhere in [the same provision]").

Congress's omission of "any" stands out even more given the legislative history, which warns: "Change an 'an' to a 'the' and you go from huge savings to huge cost." *Greater Access Hearing*, *supra*, at 119 (emphasis added). "*Change an 'an'* is exactly what the court below did in substituting "any" for "an." The result was to change the statute's meaning, in violation of "what Congress has written" in this "detailed" and

"extremely carefully crafted" statute. *Ibid.*; *Fleming*, 358 U.S. at 166.

b. Remarkably, the Federal Circuit "detect[ed] no ambiguity" that Congress, in selecting the term "an," really meant "any." Pet. 12a. "When a indefinite article is preceded and qualified by a negative," the majority reasoned, "standard grammar generally provides that 'a' means 'any.'" *Ibid.* In support, the majority cited two dictionary examples showing that "an" can be qualified with a negative to mean "any." *Ibid.* ("not a drop to drink"; "not a one") (citations omitted).

But two examples of usage do not create rules of "standard grammar." And the mere fact that "an," when qualified by a negative, *can* mean "any," does not show that it means "any" here. Cf. *Dist. of Col.* v. *Heller*, 554 U.S. 570, 588 (2008) ("the fact that [a] phrase was commonly used in a particular context does not show that it is limited to that context"). Indeed, as the dissent below noted, the examples chosen by the majority were taken from secondary definitions. Pet. 41a.

A simple illustration confirms that the meaning of "an" depends on how the word is being used. Suppose A writes to B with news that she had another child. When relating the challenges of having more children, A adds: "My taxes were higher than they should be because I did not claim an exemption." Read in context, this statement does not suggest that A did not claim *any* exemptions—only that she did not claim an exemption *for the latest child*. Any contrary reading would ignore the context.

The same is true of the Federal Circuit's reading of "an approved method" to mean "*any* approved me-

thod." Just as tax exemptions must be claimed on an individualized basis, so too must approved uses of drugs. And just as the context of A's statement makes clear that "an exemption" refers to a particular exemption, so too the context in which the counterclaim is brought (where the applicant seeks approval for a particular approved method of use) makes clear that the counterclaim provision refers to a single approved method of using the drug. See also *First Nat'l Bank of St. Louis* v. *Missouri*, 263 U.S. 640 (1924) (declining to read "an" to mean "any" in a statute providing that "the usual business of each national banking association shall be transacted at an office or banking house located in the place specified in its organization certificate"; stating, that the statute "employing, as it does, the article 'an' to qualify words in the singular number, would confine the association to one").

Other examples confirm the point. Suppose a student in a college history class with various assigned readings states: "I failed the final exam because I did not read an assigned text." One would not conclude that the student did not read *any* assigned text—only that she failed to read a particular text that turned out to be critical. Similarly, suppose a patient whose condition required taking various medicines tells his doctor: "I had to be hospitalized because I did not take a prescribed medicine." One would not naturally conclude that he failed to take *any* medicine.

We could go on—"He failed to obtain a conviction because he did not prove an element of the offense." "They lost the case because they did not address an applicable precedent." "The cake did not rise because I did not include an ingredient." "We could not close on the house because we did not complete an impor-

tant form." "I arrived at the party late because I did not make a necessary turn." None of these examples is a slight to "standard grammar." Pet. 12a. The examples violate no grammatical rules at all. They simply show that, in ordinary usage of negative assertions, whether "an" means "any" depends upon the context.

In short, inserting the categorical word "any" into the text was not a neutral interpretive decision; it changed the counterclaim's meaning. "Any" is an "expansive" and "unqualified" term (*Salinas*, 522 U.S. at 57); and as Subsection II of the counterclaim confirms, Congress knew how to say "any" in a negative assertion when it wanted to. Its decision not to include that term in the phrase "does not claim an approved method of using the drug" must therefore be respected.

2. The structure of the counterclaim, which places the burden of proof on "the ANDA applicant" and authorizes courts to order brands to "correct or delete" inaccurate patent information, further supports reversal.

This ordinary reading of "an" is confirmed by its context. *Johnson* v. *United States*, 130 S. Ct. 1265, 1270 (2010) ("[u]ltimately, context determines meaning"). It is a "fundamental principle of statutory construction * * * that the meaning of a word cannot be determined in isolation, but must be drawn from the context in which it is used." *Deal* v. *United States*, 508 U.S. 129, 132 (1993). Here, several aspects of the

immediate statutory context confirm that "an" does not mean "any."[5]

a. *First*, it is "the ANDA applicant" that bears the burden of proof under the statute. According to Novo, Caraco cannot state a counterclaim because Novo has shown "that the patent-in-suit *does* claim an approved use." Opp. 19 (emphasis added). But that is not what the counterclaim asks. It requires "the ANDA applicant" (the generic seeking "patent certainty") to show that "the patent *does not* claim * * * an approved method of using the drug." Thus, the counterclaim asks not whether the *brand* can show that its patent *does claim* "an approved method," but whether the *generic* can point to "an approved method" that the patent "*does not* claim." Ignoring this vital aspect of the Act's text and structure, Novo invites the Court to read the statute backwards—as if the counterclaim placed the burden on the brand.

Novo's reading also rests on a logical fallacy—namely, that whether the patent claims an approved method of use is necessarily an either-or proposition. Only if that were true could Novo's showing that the patent claims one approved use defeat the counterclaim. Frequently, however, a drug has multiple approved uses, and the patent-in-suit claims only a subset of those uses. In those situations, it can simultaneously be true that the patent *both* (1) "claims an

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[5] Even "'[a]ny' can and does mean different things depending on the setting." *Nixon* v. *Mo. Mun. League*, 541 U.S. 125, 132 (2004); see *Kasten*, 131 S. Ct. at 1332 (Scalia, J., dissenting) ("the modifier 'any' does not cause a word that is in context narrow to become broad. The phrase 'to cash a check at any bank' does not refer to a river bank, or even a blood bank.").

approved method of use" *and* (2) "does not claim an approved method of use." That is why the counterclaim's structure—which turns on the generic's ability to identify an approved use that the patent "does not claim"—is so important. See *Eli Lilly*, 496 U.S. at 669 (Hatch-Waxman must be read in light of "the structure of the * * * Act taken as a whole").

Congress knew that certain drugs have multiple approved uses. As the counterclaim's first phrase states, generics may bring counterclaims when, among other requirements, they are sued by "the [NDA] holder * * * for the drug that is claimed by the patent or *a* use of which is claimed by the patent." (Emphasis added). Had Congress believed that the counterclaim applied only where there was *one* approved use, it would have been far more natural for Congress to refer to "*the* use of [the drug] claimed by the patent." Similarly, generics invoking Section viii must certify that the "method of use patent * * * does not claim *a* use for which the applicant is seeking approval." 21 U.S.C. § 355(j)(2)(A)(viii) (emphasis added). Thus, there is no question that the counterclaim was designed to address situations in which the listed patent claims some, but not all, approved uses.[6]

b. *Second*, the decision below overlooks the counterclaim's phrase "*correct or* delete patent information." (Emphasis added.) In fact, that decision offered no explanation why the term "correct' is not

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[6] This conclusion is consistent with the Dictionary Act. 1 U.S.C. § 1 ("unless the context indicates otherwise," "words importing the singular include and apply to several persons, parties, or things"). By contrast, reading "an" as "any"—that is, not a single one—prevents "an" from referring to multiple unclaimed uses.

"render[ed] superfluous," in violation of basic rules of statutory construction. See *Astoria Fed. Sav. & Loan Ass'n* v. *Solimino*, 501 U.S. 104, 112 (1991).

Under the ruling below, a counterclaim is available only where the patent listed in the Orange Book claims neither the drug at issue nor any approved method of using it—the problem in the *Mylan* case. *Supra* at 13-14. As the dissent recognized, however, the patent in those cases should not be listed *at all*, and the only proper remedy is "deleting" it. Pet. 32a (Dyk, J., dissenting). If the statute were limited to this situation, Congress's reference to "correct[ing]" the brand's patent information would serve no meaningful purpose. As Judge Dyk observed: "[V]iewing [the counterclaim] as limited to complete delisting would be inconsistent with the explicit statutory language, which provides for correction of Orange Book information" as well. *Ibid.* In fact, under the ruling below, the counterclaim would be unavailable even to correct an erroneous expiration date for a patent that claims either the drug or *any* approved method of use.

This Court need not look beyond the statute's reference to "correct[ing]" patent information to see that Congress was not simply reversing *Mylan*. And even if *Mylan* had "prompted the *proposal* of [the counterclaim]," "whether that alone accounted for its *enactment* is quite a different question." *Eli Lilly*, 496 U.S. at 670 n.3. But the legislative history further confirms the textual interpretation.

The year before the counterclaim was enacted, the FTC issued an extensive, 129-page study describing myriad strategies that brands used to delay generic entry, including "improper Orange Book listings." FTC, *Generic Drug Entry Prior to Patent Expiration*

(July 2002). One solution the FTC proposed was to allow a generic to bring a counterclaim in the context of patent infringement litigation. *Id.* at v.

The legislative history contains no significant discussion of *Mylan*, but repeatedly cites the FTC study. Congress heard testimony from the FTC's chairman multiple times. As one senator noted, "to believe that the patent laws are not being abused, is to ignore the mountain of testimony from consumers, industry analysts, and the Federal Trade Commission." 149 Cong. Rec. at 15514 (statement of Sen. McCain). And as the FTC's Chairman testified, "[c]onsistent with an FTC Study recommendation, both the Senate and House bills provide generic applicants a new tool to correct patent information listed in the Orange Book." *Greater Access Hearing*, *supra*, at 114 (statement of Chmn. T. Muris).

FDA likewise urged that, to resolve problems with the scope of patent use codes, "the courts are the appropriate mechanism." 68 Fed. Reg. 36683; see 149 Cong. Rec. at 16689 (statement of Sen. Hatch) ("both the [FTC] and the [FDA] played a constructive role in attempting to end several mechanisms * * * to game the system"). "In fact, when the FDA actually talked about closing these loopholes, it was made clear that legislation would be needed to finish the job." 149 Cong. Rec. at 15516 (statement of Sen. Schumer); accord *id.* at 31200. Thus, "[t]he bill provides a critical complement to the work the FDA has done in clarifying its regulations on patent listing, but it goes much further." *Legislative and Regulatory Responses Hearing*, *supra*, at 19. Specifically, "the provisions enforce the patent listing requirements at the FDA by allowing a generic applicant * * * to file a counterclaim to have the brand drug company delist the patent *or*

correct the patent information in FDA's Orange Book." 149 Cong. Rec. at 31200 (emphasis added).

Given this history, it is fanciful to say that the term "correct" might apply "[i]f an error were made," such as listing "the wrong patent number." Opp. 23. Congress did not face a "mountain of testimony" from consumers, industry analysts, FTC, and FDA because brands were error-prone—hitting the wrong keys and listing in the Orange Book patents for products other than new drug compounds and uses. Rather, "[w]hat [Congress] saw * * * was [that] there were games being played," and it "address[ed] those issues." 149 Cong. Rec. at 15517 (statement of Sen. Gregg).

Novo cannot explain why Congress would trouble itself to create a counterclaim so that generics could obtain a court order forcing brands to correct typos—something brands already have an incentive to do.[7] And, of course, even if Congress had done so, the remedy in that circumstance would be "deleting" the patent.

* * * * *

In sum, the interpretation adopted below is foreclosed by several aspects of the Act's text and structure: The counterclaim's use of "an" rather than "any"; its provision that courts may "correct *or* delete" inaccurate patent information; its reference to "a use" rather than "the use" claimed by the patent; and the fact that Congress placed the burden on the *generic* to

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[7] Because generics' Paragraph I-IV obligations—and thus the brand's opportunity to litigate before FDA approves the generic's ANDA—extend only to listed patents (21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV)), brands have ample incentive to fix mistaken patent numbers.

identify "an approved method" that the patent "*does not* claim." The legislative history further confirms that the lower court's reading is untenable.

B. Novo's patent use code is "patent information submitted by the holder under subsections (b) or (c)" of Section 505.

The Federal Circuit further erred in holding that patent use codes are not "patent information submitted by the holder under subsection (b) or (c)" of section 505 of the FDCA. 21 U.S.C. § 355(j)(5)(C)(ii)(I). The meaning is plain. As explained below, a use code describing a patent's scope is, in fact, "information" about a "patent," and that information is submitted to the FDA under a regulation entitled "Submission of patent information."

1. The counterclaim refers to "patent information submitted under" subsections 505(b) or (c), not patent information "described in" or "prescribed by" those subsections.

Like the court below (Pet. 15a), Novo insists that the counterclaim covers "information 'submitted under (*and thus specified in*) Section 355(b) or (c)." Resp. Supp. Br. 4 (emphasis added). But the counterclaim does not say "specified in" or "described in." It says "submitted * * * under." And this language stands in contrast to other sections of the Act, which *do* refer to patent information "described in," "required under," or "prescribed by" subsections (b) or (c).[8]

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[8] *E.g.*, 21 U.S.C. § 355(c)(2) ("patent information *described in* subsection (b) * * * could not be filed with the submission of an application under subsection (b) of this section

Thus, when Congress intended to refer to the specific types of patent information described in subsection (b) or (c)—*i.e.*, patent numbers and expiration dates—it did so expressly. Yet Congress did not use such language in the counterclaim. Accord U.S. Invitation Br. 14 ("the counterclaim provision does not refer to patent information 'required by' or 'specified in' Sections 355(b) or (c), and the actual statutory language encompasses a broader range of information"). Rather, Congress used the phrase "submitted under," phrasing it used throughout the Act when referring to patent information submitted under FDA regulations.[9]

Reading the Act "as a whole," therefore, it is clear that Congress did not limit the courts' ability to correct inaccurate "patent information" to cases involving incorrect patent numbers or expiries. See *Eli Lilly*, 496 U.S. at 669 (Hatch-Waxman must be read "as a whole"); see also *Ardestani*, 502 U.S. at 135 (the

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because the application was filed before the patent information was *required under subsection (b)* of this section or a patent was issued after the application was approved under such subsection") (emphasis added); *id.* § 355(d)(6) ("If the Secretary finds * * * the application failed to contain the patent information *prescribed by* subsection (b) of this section") (emphasis added); *id.* § 355(e)(4) ("the patent information *prescribed by* subsection (c) of this section was not filed within thirty days * * *") (emphasis added).

[9] See 21 U.S.C. § 355(c)(2) ("Upon the *submission* of patent information *under* this subsection, the Secretary shall publish it.") (emphasis added); *id.* § 355(j)(5)(D)(i)(I)(bb)(CC) ("The patent information *submitted under subsection (b) or (c)* of this section is withdrawn by the holder of the application approved under subsection (b) of this section.") (emphasis added).

term "under," followed by a statutory provision, refers to regulatory proceedings subject to, or governed by, that provision). And as the United States observes: "A use code is 'patent information' within any usual understanding of that term because it is 'information'—a 'description of the patented method of use,' 21 C.F.R. § 314.53(c)(2)(ii)(P)(3)—about a 'patent.'" U.S. Invitation Br. 13.

2. Novo submitted its use code under subsections 505(b) or (c).

The patent information here also was plainly "submitted under" Sections 505(b) and (c). FDA relied on those very provisions in promulgating its regulation, entitled "Submission of patent information." 21 C.F.R. § 314.53. As FDA explained in the 2003 Final Rule, its "principal legal authority for the final rule is section 505 of the act"—in particular, "the patent submission * * * requirements" of "Section 505(b) and (c)." 68 Fed. Reg. at 36697-98.[10]

These regulations require brands to submit patent use code descriptions for method patents—*i.e.*, "[t]he description of the patented method of use as required for publication" in FDA's Orange Book. 21 C.F.R.

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[10] Citing FDA comments from *2007*, Novo suggests that the *2003* rule was based on FDA's "general rulemaking authority and subsection (j)," as opposed to subsections (b) or (c). Opp. 27. But subsection (j) refers to ANDAs, not patent submission requirements for NDA holders. Moreover, the very pages cited by Novo reiterate that "the basis for requiring a description of each individual method of use for which a patent is submitted for listing" was discussed "in the June 2003 final rule" (72 Fed. Reg. at 21268) —namely, § 505(b) and (c). And even in 2007, FDA continued to invoke § 505(b). *Id.* at 21268-21689.

§ 314.53(c)(2)(ii)(P)(3). This submission must take a particular form. *Id.* § 314.53(c)(2)(ii); see 68 Fed. Reg. at 36686 (Form 3542 "requires * * * a description of the approved methods of use"); Pet. 211a (Form 3542). As Novo's own "patent information" form states on the top, Novo's submission was "provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act":

Department of Health and Human Services Food and Drug Administration	Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 2.
PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT *For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation or Composition) and/or Method of Use*	NDA NUMBER 20-741 NAME OF APPLICANT/NDA HOLDER Novo Nordisk Inc.
The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.	
TRADE NAME Prandin	

Pet. 211a; JA97. In sum, Novo's patent use code was "submitted under" FDA's "Submission of patent information" regulations and Sections 505(b) and (c) of the Act.

3. FDA reasonably interpreted "patent information" to include use codes.

The court below concluded otherwise by misconstruing the Act as including an "express statutory definition" that limits "patent information" to "the patent number and the expiration date." Pet. 15a. But Hatch-Waxman contains no definition of "patent information," let alone such a restrictive one. 21 U.S.C. § 321 (definitions). Pursuant to subsection 505(b), brands must file patent numbers and expirations of method patents *only* if they actually "claim[] a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted." *Id.* § 355(b)(1)(G). Yet the statute provides FDA with no guidance to determine whether a me-

thod patent satisfies this criteria—a determination particularly relevant under Section viii.

Moreover, while subsection (b) states that "patent information" *includes* "the patent number and the expiration date" (*ibid.*), it does not preclude FDA from requiring "more specific information on the approved methods of use protected by a submitted patent"—which is "necessary" "[t]o effectively implement the [Paragraph IV] certification and section viii statement provisions" (68 Fed. Reg. at 36682, 36683). As FDA explained: "Only with this information can we determine what submission is required of [generics]." *Id.* at 36683. "[A]ccurate and detailed information related to the approved methods of use" is "essential" to FDA's ability to "expedite [its] review of ANDA * * * applications that do not seek approval for all the approved uses"—a statutory duty. *Id.* at 36682, 36685.

At a minimum, therefore, FDA acted reasonably in reading the Act to authorize requiring such information as part of—*i.e.*, in a "submi[ssion] under"—the NDA process set forth in 21 U.S.C. § 355(b)-(c). *Chevron, U.S.A., Inc.* v. *Natural Resources Defense Council, Inc.*, 467 U.S. 837, 843-844 (1984) (where "Congress has explicitly left a gap for an agency to fill, [and] there is an express delegation of authority to the agency to elucidate a specific provision of the statute by regulation," regulations "are given controlling weight unless * * * manifestly contrary to the statute"). Indeed, Novo has never challenged FDA's authority to promulgate its "Submission of patent information" regulations.

4. Congress ratified FDA's definition of "patent information."

Even if FDA lacked such authority in the first instance, Congress ratified the agency's "Submission of patent information" requirements when it created the counterclaim. "[O]nce an agency's statutory construction has been 'fully brought to the attention of the public and the Congress,' and the latter has not sought to alter that interpretation although it has amended the statute in other respects, then presumably the legislative intent has been correctly discerned." *United States* v. *Rutherford*, 442 U.S. 544, 554 n.10 (1979) (invoking Congress's failure to reject FDA's interpretation of the FDCA upon amending the Act as support for ratification). And as Judge Dyk explained, "Congress was well aware of [FDA's] regulatory interpretation of 'patent information' when it enacted the counterclaim provision," providing "compelling evidence of legislative adoption." Pet. 36a, 37a (collecting legislative history); accord U.S. Invitation Br. 14.

Indeed, Congress not only had constructive knowledge of FDA's reading of "patent information" under Sections 505(b) and (c); it repeatedly heard testimony about and "cited approvingly" FDA's regulations (Pet. 36a) in the course of adopting the counterclaim.[11] As

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[11] In addition to the many authorities collected by the dissent below (Pet. 36a), see 149 Cong. Rec. 31200 (statement of Sen. Schumer) ("the provisions enforce the patent listing requirements at the FDA by allowing a generic applicant to file a counterclaim to have the brand drug company delist the patent or correct the patent information in FDA's Orange Book."); *Legislative and Regulatory Responses Hearing*, *supra*, at 5-10 (statement of D. Troy, Chief Counsel for FDA); *Greater Access Hearing*, *supra*, at

the lead sponsor put it: "The bill provides a critical complement to the work the FDA has done in clarifying its regulations on patent listing, but it goes much further." *Legislative and Regulatory Responses Hearing, supra*, at 19.

Moreover, Congress was legislating in the precise area of the regulations' application, and adopted language that closely tracks the text of the regulations and Form 3542, both promulgated months earlier:

Counterclaim:	"patent information submitted by the [NDA] holder under subsection (b) or (c) of [Section 505]";
Regulation:	"Submission of patent information" by an NDA applicant "under section 505(b) of the act" (21 C.F.R. § 314.53); "patent information * * * submitted under section 505(b) or (c)" (21 C.F.R. § 314.94(a)(12)(iii)(A) and (B));
Form 3542:	"patent information submitted upon and after approval of an NDA" and "provided in accordance with Section 505(b) and (c) of the [FDCA]" (Pet. 211a).

As a comparison of the text of these authorities confirms, Congress's use of the phrase "patent information submitted under" was no coincidence. Rather, Congress knew about, was referring to, and by

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7-10 (same). In fact, FDA has required brands to submit more than patent numbers and expiries since 1994. See 59 Fed. Reg. 50338, 50363 (Oct. 3, 1994) (promulgating rules requiring submission of, among other things, a declaration that the patent covers a drug or its approved use).

adopting parallel language ratified FDA's "Submission of patent information" regulations, which describe in detail what "patent information" is, and how it is to be "submitted." 21 C.F.R. § 314.53. It is difficult to imagine a clearer case of ratification.

C. The counterclaim should not be read to permit brands to thwart competition by eviscerating Section viii and effectively extending the scope of their patents.

As we have shown, the Federal Circuit's readings of the phrases "an approved method" and "patent information" are foreclosed by the Act's text, structure, and extensive legislative history. Reversal is also warranted, however, because those readings contravene the broader structure and purpose of the Act and the patent laws. Indeed, it is no exaggeration to say that the decision below leads to absurd results—effectively writing Section viii out of the statute, eliminating the remedy of "correcting" patent information, and licensing brands to block non-infringing generic competition under a law designed to promote such competition.

By limiting the counterclaim to cases in which the brand's patent does not claim "*any* approved use" of the drug, the ruling below "eviscerates Section viii"—"a critical provision" that "facilitates the approval and marketing of lower-cost generic drugs for uses no longer protected by a patent." Pet. 62a, 59a (Gajarsa, J., dissenting). Brands are now free to use their patents to block the sale of generic drugs that concededly do not infringe—effectively extending their limited method-of-use patents "to unpatented uses." *Id.* at 62a. That would be extraordinary under any statute, but it is particularly troubling under a law designed

to create "patent certainty" (21 U.S.C. § 355(j)(5)(C)(ii)(I)) and expedite generic competition. As Judge Gajarsa put it, that Caraco must "wait to launch its generic repaglinide product until 2018, the date on which Novo's '358 patent on the combination therapy expires—despite the fact that the '358 patent concededly does not cover the use for which Caraco seeks to market the drug"—"is an untenable and absurd result." Pet. 63a.

The Act does not require such a result. Rather, Section viii and the counterclaim were "meant generally to be complementary," and this Court's Hatch-Waxman precedent requires that they be read that way. *Eli Lilly*, 496 U.S. at 673-674.

1. The ruling below threatens to eviscerate Section viii.

Section viii enables generics to avoid infringement litigation where, as here, the generic seeks to market its drug solely for non-infringing uses. The ruling below, however, effectively "render[s] Section viii a dead letter" (Fet. 62a), in violation of the basic rule that "[a] statute should be construed so that effect is given to all its provisions, so that no part will be inoperative or superfluous, void or insignificant." *Corley*, 129 S. Ct. at 1566 (quoting *Hibbs* v. *Winn*, 542 U.S. 88, 101 (2004)).

a. When a generic files a Paragraph IV certification, that constitutes an artificial act of infringement that obligates the brand either to sue or risk FDA approval of generic marketing. 35 U.S.C. § 271(e)(2). If the brand sues, FDA approval is generally stayed for 30 months or until the generic prevails—in which case FDA may approve the ANDA. 21 U.S.C. § 355(j)(5)(B)(iii). Further, if the generic is the first

ANDA filer, it is eligible for 180 days of market exclusivity before other generics can enter the market. *Id.* § 355(j)(5)(B)(iv). But generics must generally prevail in court to obtain FDA approval under Paragraph IV.

Section viii, by contrast, is designed to avoid litigation. It "facilitates the approval and marketing of lower-cost generic drugs for uses no longer protected by a patent." Pet. 59a. Where the patent information submitted by the brand asserts that "a patent claims at least one, but not all, approved methods of using a drug" (Pet. 13a), Section viii allows the generic to certify that the patent "does not claim a use for which the applicant is seeking approval." 21 U.S.C. § 355(j)(2)(A)(viii). The generic may submit carved-out labeling that does not refer to the patented uses (Pet. 6a); and if the FDA approves it, litigation is unnecessary. But even if it is the first Section viii filer, a generic cannot obtain 180 days of marketing exclusivity under Section viii.

Paragraph IV and Section viii thus offer tradeoffs. Prevailing in Paragraph IV suits holds the promise of a non-infringement or invalidity ruling—enabling the generic to sell its drug for *all* approved uses—and for first filers 180 days of marketing exclusivity. Section viii offers only the ability to market drugs for *some* approved uses, with no prospect of marketing exclusivity. Yet Section viii avoids the "hazard[s] of sparking costly litigation." *Teva Pharms. USA, Inc.* v. *Sebelius*, 595 F.3d 1303, 1305 (D.C. Cir. 2010). It is therefore "essential to the [Act's] operation." Pet. 29a.

b. The decision below "eviscerates Section viii." Pet. 62a (Gajarsa, J., dissenting). The ruling creates

"every incentive" for brands "to follow Novo's lead and draft exceedingly broad use codes," "thereby insulating themselves from generic competition." *Ibid.*

Overbroad use codes eliminate the option of using Section viii. Normally, a generic drug's labeling must be "the same as the labeling approved for the [branded] drug." 21 U.S.C. § 355(j)(2)(A)(v). FDA will thus accept proposed carved-out labeling only if it can determine that the proposed labeling avoids the patent as described in the brand's use code. Pet. 6a. An overbroad use code makes that impossible. As a result, generics can reach the market early only through protracted Paragraph IV litigation—where their approval will depend on proving patent *invalidity*—when they should not even have to litigate.

To be sure, even without Section viii, some generics might reach the market by winning a Paragraph IV suit. But the point of Section viii is that a generic should not have to litigate *at all*, because carved-out labeling altogether avoids infringement. Being forced to litigate is thus a direct affront to Congress's ultimate goal of "get[ting] generic drugs into the hands of patients at reasonable prices—fast." *Barr Labs.*, 930 F.2d at 76. And delaying the sale of what otherwise would be *concededly* non-infringing drugs while generics litigate patent validity is an "absurd result." Pet. 63a.

c. Moreover, by eliminating the Act's check on allowing brands to overstate their patents, the decision below "effectively allows a patent holder to extend its monopoly to unpatented uses." Pet. 62a. This is especially troubling under Hatch-Waxman. In other markets, competitors that wish to market allegedly infringing products can launch at risk and litigate

later. But marketing drugs requires FDA approval. *Eli Lilly*, 496 U.S. at 670-671. Thus, if brands can bottle up the approval process, generics are excluded from the market even where there is concededly no risk of infringement. The counterclaim prevents such "gam[ing] of the system," but the ruling below renders that provision "a virtual nullity." Pet. 59a, 60a.

In sum, the fractured decision below gives brands "another way to game the system." Pet. 60a (Gajarsa, J., dissenting). Brands "now have every incentive" to "submit[] overbroad and inaccurate use codes," thus "subverting [generics'] carve-out statements," "delaying the onset of generic competition," and "rendering Section viii a dead letter." *Id.* at 60a, 62a.

2. *Eli Lilly* requires "strong evidence" to support reading the Act to permit an effective expansion of a patent's scope, and such evidence is absent here.

Structural problems such as these, which effectively expand the reach of a patent, are telltale signs of misinterpretation under *Eli Lilly*. There, faced with a Hatch-Waxman provision that (unlike the counterclaim) was "not plainly comprehensible on anyone's view," this Court turned to "the structure of the 1984 Act taken as a whole." 496 U.S. at 669; accord *FDA* v. *Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000) ("A court must * * * interpret the statute as a symmetrical and coherent regulatory scheme and fit, if possible, all parts into a harmonious whole.") (citations and quotation marks omitted). A similar analysis requires reversal here.

In *Lilly*, the Court considered the safe harbor of 35 U.S.C. § 271(e)(1), which exempts from patent in-

fringement the use of "a patented invention * * * for uses reasonably related to the development and submission of information" to FDA "under a Federal law which regulates the manufacture, use, or sale of drugs." The question was whether this safe harbor extended to medical devices. The answer would be no, of course, if "a Federal law" referred "to those individual provisions of federal law that regulate drugs." 496 U.S. at 665. But devices would be covered if "a Federal law" referred to "the entirety of any Act * * * at least some of whose provisions regulate drugs." *Id.* at 665-666.

Given conflicting textual signals, the Court chose the reading that best "fit" Hatch-Waxman's provisions together to cure twin patent-term "distortions" targeted by Congress. *Id.* at 674. On the one hand, during a patent's infancy, a manufacturer might spend years developing a device and waiting for FDA approval; on the other hand, as the patent aged, competitors were forced to wait for the patent's expiration even to begin research and development. *Id.* at 670-671. To correct these "dual distorting effects," the Court observed, Hatch-Waxman established, on the front end, a term extension for patents relating to products subject to lengthy regulatory delays and, on the back end, a safe harbor for experimentation. *Id.* at 672. Since these provisions were "meant generally to be complementary," the Court was not surprised that "[a]ll of the products eligible for a patent term extension" were "subject to [the safe harbor]." *Id.* at 673-674.

Because makers of devices were expressly entitled to the term extension on the front end, the Court held that competitors were implicitly covered by the safe harbor on the back end. That is, the Court chose the

reading of the safe harbor provision that "*appears to create a perfect 'product' fit between the two sections.*" *Id.* at 674 (emphasis added). To do otherwise, the Court explained, would "leave in place an anticompetitive restriction at the end of the monopoly term" and "simultaneously expand the monopoly term itself." *Id.* at 672. "It would take strong evidence to persuade us that this is what Congress wrought, and there is no such evidence here." *Id.* at 673.

Like the patent-term extension and safe harbor in *Eli Lilly*, Section viii and the counterclaim were "meant generally to be complementary." *Ibid.* Indeed, Section viii cannot function properly apart from the counterclaim, which precludes brands from thwarting Section viii carve-outs by filing overbroad patent use codes. *Supra* at 42-45. Therefore, the Court should read the counterclaim to create a "fit between the two sections." 496 U.S. at 674. This means reading "an" to mean "an," "patent information" to mean what Congress and FDA said it means, and "correct" to have teeth. Otherwise, a brand can effectively "extend its monopoly to unpatented uses." Pet. 62a. As in *Eli Lilly*, it "take[s] strong evidence to persuade us that this is what Congress wrought, and there is no such evidence here." *Id.* at 673.

In sum, to construe the counterclaim as the court below construed it, "one must posit" both "a good deal of legislative imprecision" and "an implausible substantive intent as well." *Id.* at 679. This Court should not read the Hatch-Waxman Act that way. *Ibid.*

II. Caraco is entitled to an order enjoining Novo to reinstate its original patent use code.

As we have explained, Novo's '358 patent *does not* claim an approved use of repaglinide (indeed, it does

not claim two approved uses). Yet the parties are in Paragraph IV litigation precisely because Novo's use code led FDA to believe that its patent *does* claim those approved uses of repaglinide. By definition, therefore, Novo's patent use code is incorrect, and Caraco's counterclaim warrants entry of an injunction requiring its correction.

A. Having satisfied the requirements of the counterclaim, Caraco is entitled to an injunction.

Where a generic manufacturer shows that "the patent does not claim * * * an approved method of using the drug," the counterclaim authorizes courts, on that basis, to enter "an order requiring the [patent] holder to *correct* or delete the patent information submitted by the holder." 21 U.S.C. § 355(j)(5)(C)(ii)(I) (emphasis added). Thus, "correct" does not describe a *standard* to avoid liability under the counterclaim; it prescribes a *remedy* that becomes available once the counterclaim has been satisfied. And because Caraco has satisfied the counterclaim, it is entitled to an injunction requiring that Novo's use code be brought into conformity with the scope of its patent. As the United States encapsulates the framework: "An order to 'correct or delete' * * * patent information is appropriate * * * if the use code misleadingly suggests that the patent claims approved methods of use that it does not actually cover." U.S. Invitation Br. 12.

It follows that Novo cannot be heard to say that, even if the counterclaim has been satisfied, nothing needs correcting. *E.g.*, Opp. 30-31. As we have shown, Novo is blocking Caraco's Section viii carved-out labeling by describing its patent in an overbroad

manner. Caraco was compelled to invoke the counterclaim to show the discrepancy between Novo's patent and its use code. Having successfully done so, Novo's Orange Book listing necessarily requires correcting.

The remedy is simple—restore Novo's original use code. Novo does not dispute that this description of its patent—"use of repaglinide in combination with metformin to lower blood glucose" (JA99)—was correct. Indeed, to this day Novo uses this precise language to describe the '358 patent in reference to its repaglinide-metformin combination product. JA52, 549 (use code U-546). Thus, this Court need only reinstate the district court's injunction requiring Novo to resubmit its original use code.

B. Under the ordinary meaning, structure, and purpose of the Hatch-Waxman Act's counterclaim provision, Novo's patent use code was not "correct."

Even if "correct" described a standard for avoiding liability under the counterclaim, rather than a remedy for satisfying the counterclaim, this Court should still enjoin Novo to correct its patent use code. Under any reasonable standard, that use code is incorrect.

1. "Correct" means "to make or set right" and "to alter or adjust so as to bring to some standard or required condition." *Webster's Ninth New Collegiate Dictionary* 293 (1983). By the statute's terms, therefore, courts may order that a brand's patent information be "set right" or "altered" to "bring [it] to some standard or required condition." *Ibid.*

The counterclaim itself provides the standard: The brand's patent information must inform the reader which "approved method[s] of using the drug"

the brand's patent "does not claim." 21 U.S.C. § 355(j)(5)(C)(ii)(I). And the point of the required use code is to describe the patent's scope, so FDA and generics can determine whether infringing uses may be carved out from the generic's labeling.

As the district court found, Novo's expanded use code—first submitted when FDA agreed to approve Caraco's Section viii statement—"is so broad as to incorrectly suggest that its patent generically covers three (3) different FDA-approved methods of use," when "it admits that the first two (2) uses are not covered." Pet. 68a. Accordingly, Novo's use code must be "corrected" to enable FDA and generics to tell that the '358 patent "does not claim" repaglinide as monotherapy or repaglinide in combination with TZDs—each of which is "an approved method of using the drug." No fact-finding or legal analysis is required.

Novo's original use code—which described its patent as covering only the "use of repaglinide in combination with metformin to lower blood glucose" (Pet. 44a; JA99)—was "correct" under this standard. It informed interested parties that the '358 patent "does not claim an approved method of using the drug" repaglinide, facilitating FDA's review and approval of Caraco's Section viii carve-out labeling.

The same cannot be said of Novo's newly minted use code: "a method for improving glycemic control in adults with type 2 diabetes mellitus." Pet. 45a. That use code "seriously misrepresents the approved method of use covered by [the patent]." Pet. 70a. The original use code should be ordered reinstated.

2. Faced with the ordinary meaning of "correct," the most Novo can say is that "[t]he counterclaim gives the [courts] no license to force Novo to choose

between two truthful alternatives." Opp. 30. This is sophistry. The counterclaim's applicability is not triggered by a submission to FDA that is "untrue" or "false" in some hyper-literal or abstract sense. Indeed, in contrast to other provisions of the Act, the counterclaim does not turn on whether the brand makes "an untrue statement of material fact" (21 U.S.C. § 355(j)(4)(K)) or a statement that is "false or misleading in any particular" (*id.* § 355(d)(7)). It turns on whether the information is "correct" in light of what the brand's patent "does not claim."

But even if truth were the standard, Novo's use code could not fairly be described as truthful. "[T]he meaning of a word cannot be determined in isolation, but must be drawn from the context in which it is used." *Deal*, 508 U.S. at 132. A patent is a property right, and "patent claims" define the "boundary of the patent monopoly." *Gen. Foods Corp.* v. *Studiengesellschaft Kohle*, 972 F.2d 1272, 1274 (Fed. Cir. 1992) (citation and quotation marks omitted)). Thus, this Court has "liken[ed] patent claims to the description of real property in a deed 'which sets the bounds to the grant which it contains.'" *Ibid.* (quoting *Motion Picture Patents Co.* v. *Universal Film Mfg. Co.*, 423 U.S. 502, 510 (1917)). And no one would reasonably defend as "truthful" a landowner's claim that he owned more land than his deed indicates.

So too here. When a statute creates a cause of action to "correct" patent information that fails to describe what a patent "does not claim," it is neither "truthful" nor "correct" to describe what the patent does claim in an overbroad way. Otherwise, brands could routinely submit patent use codes claiming "a method of treating disease," thereby blocking possible carved-out labeling under any circumstance. That is

not sensible, particularly considering the meaning of the term "patent claim" and the point of the use code exercise—to describe the scope of the patent.

3. The surrounding text, statutory structure, and overall purpose of the counterclaim all confirm that whether "patent information" is "correct" for purposes of the counterclaim depends on whether it identifies the "approved method of use" that the related patent "does not claim." Cf. *Sullivan*, 494 U.S. at 90 (looking to "fuller context" of statute to define "correct amount"). In light of the history of the 2003 amendments, the term "correct" signals Congress's intent to give generics a judicial remedy for the games brands have played with Orange Book patent information. *Supra* at 30-33. The natural reading of "correct" also fits precisely with Congress's express purpose. By enabling both FDA and generics to tell what a patent "does not claim," that reading promotes "patent certainty." 21 U.S.C. § 355(j)(5)(C)(ii)(I).

But even if the term "correct" reflected "legislative imprecision" (*Eli Lilly*, 496 U.S. at 679), Novo could not explain why Congress would want courts to order "deleting" misleading patent information when brands' patents claim *no* approved use, but not "correcting" misleading patent information for *some subset of* approved uses. One tactic blocks generic marketing as well as another. And "submission of an overbroad or otherwise misleading use code can cause the same practical harm (unjustified delay in a generic drug's entry into the market) as does the listing of a patent that claims *no* approved uses of the relevant drug." U.S. Invitation Br. 16.

C. FDA's regulations confirm that, to be "correct," the patent use code must be accurate, detailed, and tailored to the patent's scope.

The ordinary reading of "correct" is confirmed by FDA's regulations, which Congress ratified in adopting the counterclaim provision. *Supra* at 39-41.

1. In promulgating the 2003 Final Rule, FDA repeatedly insisted that, to serve its statutory purpose, "the description of the approved use" must be "accurate and detailed." 68 Fed. Reg. at 36682.[12] As FDA explained, "it is necessary that an NDA holder submit more specific information on the approved methods of use protected by a submitted patent. Only with this information can we determine what submission is required of the ANDA * * * applicants referencing the approved drug." *Id.* at 36683.

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[12] *E.g.*, 68 Fed. Reg. at 36682 ("[W]e do require identification of individual claims for method-of-use patents," as "[t]his information will expedite our review of ANDA * * * applications that do not seek approval for all the approved uses. In determining whether an ANDA applicant can 'carve out' the method of use * * * we will rely on the description of the approved use provided by the NDA holder"); *ibid.* ("[FDA] require[s] the NDA applicant or holder to identify specifically the approved uses claimed by the method-of-use patent, with reference to the approved labeling," which "permit[s] ANDA * * * applicants, and us, to assess whether the ANDA * * * applicant is seeking approval for a use the sponsor states is claimed in the listed patent, and thus determine whether the applicant must submit a [Paragraph IV] patent certification or may submit a section viii statement").

Accordingly, FDA regulations require brand-name manufacturers to state "[w]hether the patent claims one or more approved methods of using the approved drug product *and* a description of *each* approved method of use or indication *and related patent claim* of the patent being submitted." 21 C.F.R. § 314.53 (c)(2)(ii)(P)(1) (emphasis added). Additionally, brands must "identif[y] * * * the specific section of the approved labeling for the drug product that corresponds to the method of use claimed by the patent submitted; and * * * [*t*]*he description of the patented method of use.*" *Id.* § 314.53 (c)(2)(ii)(P)(2)-(3) (emphasis added). As the instructions for Form 3542 state: "Each approved use claimed by the patent should be separately identified * * * and contain adequate information to assist * * * ANDA applicants in determining whether a listed method of use patent claims a use for which the * * * ANDA is not seeking approval." Pet. 214a. And brands must certify the accuracy of their submissions under penalty of perjury. Pet. 213a.

Judged by the "standard" or "required condition" of these regulatory requirements (*Webster's, supra*), Novo's patent information is not "correct." The relevant claim of the '358 patent describes a specific method of treatment: "A method for treating non-insulin dependent diabetes mellitus (NIDDM) *comprising administering to a patient in need of such treatment repaglinide in combination with metformin.*" JA96 (emphasis added). By contrast, Novo's use code states generally: "a method for improving glycemic control in adults with type 2 diabetes mellitus." Pet. 45a. That submission does not provide a meaningful "description of the patented method of

use" that is "related" to the "approved method of use or indication."[13]

2. Having failed to satisfy FDA's straightforward tailoring requirement, Novo maintains that FDA allows a brand "to base its use code narrative on the approved method of use *or* indication for the drug." Opp. 30-31. Brands need not characterize the patent at all, the argument goes, so long as the description "tracks the approved indication." Opp. 31. But if that were true, there would no point to providing use codes, because they would reveal nothing about the patent's scope.

Nor is that what the regulation says. If a brand relies on an indication, the regulation requires the brand to tie that indication to the "related patent claim" by identifying "the specific section of the approved labeling * * * that corresponds to the method of use claimed by the patent submitted; and * * * [t]he description of the patented method of use." 21 C.F.R. § 314.53(c)(2)(ii)(P)(1)-(3). As the district court noted, FDA requires use codes to "accurately describe each approved method of use *claimed* by a patent listed in the Orange Book. The narrative is limited to those approved uses of the drug product that the patent claims." Pet. 93a. But while Novo's patent use code loosely tracks Prandin's indication, the '358 patent does not claim that indication. Indeed, the indication bears no relation to the patent. Thus, for Novo's use code to be "correct," more specificity was re-

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[13] Although Prandin now has one only indication, the label still lists three distinct, approved uses: (1) as monotherapy; (2) in combination with TZDs; and (3) in combination with metformin. JA278-282.

quired—language showing *which* approved use is claimed by the patent. See 68 Fed. Reg. at 36682.

3. Aware of this difficulty, Novo attempts to pass the buck to FDA, which in 2007 required changes to the labeling of diabetes drugs, including Prandin. Opp. 31; see also Pet. 47a (Dyk, J.) (discussing this history); Pet. 20a (Clevenger, J.) (suggesting that FDA "gummed up the works"). But labels and use codes are two different things. As Judge Dyk explained, "absolutely nothing in the statute or regulations * * * required Novo to change the use code to track this new indication." Pet. 47a-48a. Indeed, at oral argument below, Novo admitted that "FDA did not direct or request that Novo change its use code to reflect the new indication, nor was Novo required under FDA regulations to make such a change." Pet. 48a (citing oral argument transcript).

As FDA wrote to Novo in 2009, patent use codes remain critical to the agency's ability to administer the statute: FDA "relies on [patentees] to craft an accurate and complete description of the relevant patent claims (to form the basis of the use code) and to identify the approved labeling that corresponds to those claims." JA372. FDA "determines which labeling corresponds to a submitted patent (and thus which labeling may be available to carve out) by relying on the use code for that patent submitted by the sponsor." *Ibid.* This correspondence leaves no room for interpretation. FDA never asked Novo to change its patent use code. Instead, it consistently required Novo to describe its patent accurately and precisely, to facilitate evaluation of Section viii ANDAs. Nor is there any way to construe this correspondence as authorizing a patent use code that merely tracks a labeled indication that the '358 patent does not claim.

* * * * *

In sum, FDA's "patent information" regulatory requirements confirm what is required by the counterclaim's text: The brand's "patent information" must reveal what its patent "does not claim." Because Novo's patent use code fails to do so, it requires correction. Thus, the Court should reinstate the district court's injunction.

CONCLUSION

For the foregoing reasons, the judgment of the court of appeals should be reversed and the district court's injunction reinstated.

Respectfully submitted.

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APPENDIX

UNITED STATES CODE

Title 21—Food and Drugs

Chapter 9—Federal Food, Drug, and Cosmetic Act

Subchapter V—Drugs and Devices

Part A—Drugs and Devices

§ 355. New drugs

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling

proposed to be used for such drug, and (G) any assessments required under section 355c of this title. The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A).

(2) An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from

the person by or for whom the investigations were conducted shall also include—

(A) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (c) of this section—

(i) that such patent information has not been filed,

(ii) that such patent has expired,

(iii) of the date on which such patent will expire, or

(iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(B) if with respect to the drug for which investigations described in paragraph (1)(A) were conducted information was filed under paragraph (1) or subsection (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

(3) Notice of opinion that patent is invalid or will not be infringed

(A) Agreement to give notice—An applicant that makes a certification described in paragraph (2)(A)(iv) shall include in the application a statement that the applicant will give notice as required by this paragraph.

(B) Timing of Notice—An applicant that makes a certification described in paragraph (2)(A)(iv) shall give notice as required under this paragraph—

(i) if the certification is in the application, not later than 20 days after the date of the postmark on the notice with which the Secretary informs the applicant that the application has been filed; or

(ii) if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.

(C) Recipients of Notice—An applicant required under this paragraph to give notice shall give notice to—

(i) each owner of the patent that is the subject of the certification (or a representative of the owner designated to receive such a notice); and

(ii) the holder of the approved application under this subsection for the drug that is claimed by the patent or a use of which is claimed by the patent (or a representative of the holder designated to receive such a notice).

(D) Contents of Notice—A notice required under this paragraph shall—

(i) state that an application that contains data from bioavailability or bioequivalence studies has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification; and

(ii) include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.

(4)(A) An applicant may not amend or supplement an application referred to in paragraph (2) to seek approval of a drug that is a different drug than the drug identified in the application as submitted to the Secretary.

(B) With respect to the drug for which such an application is submitted, nothing in this subsection or subsection (c)(3) of this section prohibits an applicant from amending or supplementing the applica-

tion to seek approval of a different strength.

(5)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1) or under section 262 of Title 42, which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection or section 262 of Title 42 if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim or, with respect to an applicant for approval of a biological product under section 262(k) of Title 42, any necessary clinical study or studies. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of the clinical trials. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant upon request.

(C) Any agreement regarding the parameters of the design and size of clinical trials of a

new drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except—

(i) with the written agreement of the sponsor or applicant; or

(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance division personnel unless such field or compliance division personnel demonstrate to the reviewing division why such decision should be modified.

(F) No action by the reviewing division may be delayed because of the unavailability

of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection or section 262 of Title 42 (including all scientific and medical matters, chemistry, manufacturing, and controls).

(6) An application submitted under this subsection shall be accompanied by the certification required under section 282(j)(5)(B) of Title 42. Such certification shall not be considered an element of such application.

(c) Period for approval of application; period for, notice, and expedition of hearing; period for issuance of order

(1) Within one hundred and eighty days after the filing of an application under subsection (b) of this section, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(A) Approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) of this section applies, or

(B) Give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) of this section on the question whether such application is ap-

provable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(2) If the patent information described in subsection (b) of this section could not be filed with the submission of an application under subsection (b) of this section because the application was filed before the patent information was required under subsection (b) of this section or a patent was issued after the application was approved under such subsection, the holder of an approved application shall file with the Secretary the patent number and the expiration date of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If the holder of an approved application could not file patent information under subsection (b) of this section because it was not required at the time the application was approved, the holder shall file such information under this subsection not later than thir-

ty days after September 24, 1984, and if the holder of an approved application could not file patent information under subsection (b) of this section because no patent had been issued when an application was filed or approved, the holder shall file such information under this subsection not later than thirty days after the date the patent involved is issued. Upon the submission of patent information under this subsection, the Secretary shall publish it.

(3) The approval of an application filed under subsection (b) of this section which contains a certification required by paragraph (2) of such subsection shall be made effective on the last applicable date determined by applying the following to each certification made under subsection (b)(2)(A) of this section:

(A) If the applicant only made a certification described in clause (i) or (ii) of subsection (b)(2)(A) of this section or in both such clauses, the approval may be made effective immediately.

(B) If the applicant made a certification described in clause (iii) of subsection (b)(2)(A) of this section, the approval may be made effective on the date certified under clause (iii).

(C) If the applicant made a certification described in clause (iv) of subsection (b)(2)(A) of this section, the approval shall be made effective immediately unless, before the expiration of 45 days after the date on which the notice described in

subsection (b)(3) of this section is received, an action is brought for infringement of the patent that is the subject of the certification and for which information was submitted to the Secretary under paragraph (2) or subsection (b)(1) of this section before the date on which the application (excluding an amendment or supplement to the application) was submitted. If such an action is brought before the expiration of such days, the approval may be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under subsection (b)(3) of this section or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that—

(i) if before the expiration of such period the district court decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the approval shall be made effective on—

(I) the date on which the court enters judgment reflecting the decision; or

(II) the date of a settlement order or consent decree signed and entered by the court stating that the

patent that is the subject of the certification is invalid or not infringed;

(ii) if before the expiration of such period the district court decides that the patent has been infringed—

(I) if the judgment of the district court is appealed, the approval shall be made effective on—

(aa) the date on which the court of appeals decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity); or

(bb) the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid or not infringed; or

(II) if the judgment of the district court is not appealed or is affirmed, the approval shall be made effective on the date specified by the district court in a court order under section 271(e)(4)(A) of Title 35;

(iii) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant

from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective as provided in clause (i); or

(iv) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent has been infringed, the approval shall be made effective as provided in clause (ii).

In such an action, each of the parties shall reasonably cooperate in expediting the action.

(D) Civil action to obtain patent certainty

(i) Declaratory judgment absent infringement action

(I) In general—No action may be brought under section 2201 of Title 28, by an applicant referred to in subsection (b)(2) of this section for a declaratory judgment with respect to a patent which is the subject of the certification referred to in subparagraph (C) unless—

(aa) the 45-day period referred to in such subparagraph has expired;

(bb) neither the owner of such patent nor the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brought a civil action against the applicant for infringement of the patent before the expiration of such period; and

(cc) in any case in which the notice provided under paragraph (2)(B) relates to noninfringement, the notice was accompanied by a document described in subclause (III).

(II) Filing of civil action—If the conditions described in items (aa), (bb), and as applicable, (cc) of subclause (I) have been met, the applicant referred to in such subclause may, in accordance with section 2201 of Title 28, bring a civil action under such section against the owner or holder referred to in such subclause (but not against any owner or holder that has brought such a civil action against the applicant, unless that civil action was dismissed

without prejudice) for a declaratory judgment that the patent is invalid or will not be infringed by the drug for which the applicant seeks approval, except that such civil action may be brought for a declaratory judgment that the patent will not be infringed only in a case in which the condition described in subclause (I)(cc) is applicable. A civil action referred to in this subclause shall be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

(III) Offer of confidential access to application—For purposes of subclause (I)(cc), the document described in this subclause is a document providing an offer of confidential access to the application that is in the custody of the applicant referred to in subsection (b)(2) of this section for the purpose of determining whether an action referred to in subparagraph (C) should be brought. The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered

for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under subsection (b)(2)(A)(iv) of this section and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement.

(ii) Counterclaim to infringement action

(I) In general—If an owner of the patent or the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) of this section or this subsection on the ground that the patent does not claim either—

(aa) the drug for which the application was approved; or

(bb) an approved method of using the drug.

(II) No independent cause of action—Subclause (I) does not authorize the assertion of a claim described in subclause (I) in any civil action or proceeding other than a counterclaim described in subclause (I).

(iii) No damages—An applicant shall not be entitled to damages in a civil action under clause (i) or a counterclaim under clause (ii).

(E)(i) If an application (other than an abbreviated new drug application) submitted under subsection (b) of

this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of another application for a drug for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted effective before the expiration of ten years from the date of the approval of the application previously approved under subsection (b) of this section.

(ii) If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application which refers to the drug for which the subsection (b) application was submitted and for which the in-

vestigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted may be submitted under subsection (b) of this section before the expiration of five years from the date of the approval of the application under subsection (b) of this section, except that such an application may be submitted under subsection (b) of this section after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in clause (iv) of subsection (b)(2)(A) of this section. The approval of such an application shall be made effective in accordance with this paragraph except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (C) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of ap-

proval of the subsection (b) application.

(iii) If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) of this section for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

(iv) If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailabilty[1] studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under subsection (b) of this section for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

(v) If an application (or supplement to an application) submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b) of this section, was ap-

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[1] So in original. Probably should be "bioavailability."

proved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection and for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted and which refers to the drug for which the subsection (b) application was submitted effective before the expiration of two years from September 24, 1984.

(4) A drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the drug and to obtain approval for the drug prior to manufacture of the drug in a larger facility, unless the Secretary makes a determination that a full scale production facility is necessary to ensure the safety or effectiveness of the drug.

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investiga-

tions, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the patent information prescribed by subsection (b) of this section; or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled

investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence.

(e) Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the

basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) the patent information prescribed by subsection (c) of this section was not filed within thirty days after the receipt of written notice from the Secretary specifying the failure to file such information; or (5) that the application contains any untrue statement of a material fact: Provided, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application submitted under subsection (b) or (j) of this section with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (k) of this section or to comply with the notice requirements of section 360(k)(2) of this title, or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information

before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based. The Secretary may withdraw the approval of an application submitted under this section, or suspend the approval of such an application, as provided under this subsection, without first ordering the applicant to submit an assessment of the approved risk evaluation and mitigation strategy for the drug under section 355-1(g)(2)(D) of this title.

(f) Revocation of order refusing, withdrawing or suspending approval of application

Whenever the Secretary finds that the facts so require, he shall revoke any previous order under subsection (d) or (e) of this section refusing, withdrawing, or suspending approval of an application and shall approve such application or reinstate such approval, as may be appropriate.

(g) Service of orders

Orders of the Secretary issued under this section shall be served (1) in person by any officer or employee of the Department designated by the Secretary or (2) by mailing the order by registered mail or by certified mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) Appeal from order

An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of Title 28. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any

person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of Title 28. The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

(i) Exemptions of drugs for research; discretionary and mandatory conditions; direct reports to Secretary

(1) The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of

the public health, provide for conditioning such exemption upon—

(A) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing;

(B) the manufacturer or the sponsor of the investigation of a new drug proposed to be distributed to investigators for clinical testing obtaining a signed agreement from each of such investigators that patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to him, and that he will not supply such drug to any other investigator, or to clinics, for administration to human beings;

(C) the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b) of this section; and

(D) the submission to the Secretary by the manufacturer or the sponsor of the investigation of a new drug of a statement of intent regarding whether the manufacturer or sponsor has plans for assessing pediatric safety and efficacy.

(2) Subject to paragraph (3), a clinical investigation of a new drug may begin 30 days after the Secretary has received from the manufacturer or sponsor of the investigation a submission containing such information about the drug and the clinical investigation, including—

(A) information on design of the investigation and adequate reports of basic information, certified by the applicant to be accurate reports, necessary to assess the safety of the drug for use in clinical investigation; and

(B) adequate information on the chemistry and manufacturing of the drug, controls available for the drug, and primary data tabulations from animal or human studies.

(3)(A) At any time, the Secretary may prohibit the sponsor of an investigation from conducting the investigation (referred to in this paragraph as a "clinical hold") if the Secretary makes a determination described in subparagraph (B). The Secretary shall specify the basis for the clinical hold, including the specific information available to the Secretary which served

as the basis for such clinical hold, and confirm such determination in writing.

(B) For purposes of subparagraph (A), a determination described in this subparagraph with respect to a clinical hold is that—

(i) the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation, taking into account the qualifications of the clinical investigators, information about the drug, the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved; or

(ii) the clinical hold should be issued for such other reasons as the Secretary may by regulation establish (including reasons established by regulation before November 21, 1997).

(C) Any written request to the Secretary from the sponsor of an investigation that a clinical hold be removed shall receive a decision, in writing and specifying the reasons therefor, within 30 days after receipt of such request. Any such request shall include sufficient information to support the removal of such clinical hold.

(4) Regulations under paragraph (1) shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using

such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where it is not feasible or it is contrary to the best interests of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs. The Secretary shall update such regulations to require inclusion in the informed consent documents and process a statement that clinical trial information for such clinical investigation has been or will be submitted for inclusion in the registry data bank pursuant to subsection (j) of section 282 of Title 42.

(j) Abbreviated new drug applications

(1) Any person may file with the Secretary an abbreviated application for the approval of a new drug.

(2)(A) An abbreviated application for a new drug shall contain—

(i) information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed under paragraph (7) (hereinafter in

this subsection referred to as a "listed drug");

(ii)(I) if the listed drug referred to in clause (i) has only one active ingredient, information to show that the active ingredient of the new drug is the same as that of the listed drug;

(II) if the listed drug referred to in clause (i) has more than one active ingredient, information to show that the active ingredients of the new drug are the same as those of the listed drug, or

(III) if the listed drug referred to in clause (i) has more than one active ingredient and if one of the active ingredients of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the other active ingredients of the new drug are the same as the active ingredients of the listed drug, information to show that the different active ingredient is an active ingredient of a listed drug or of a drug which does not meet the requirements of section 321(p) of this title, and such other information respecting the different active ingredient with respect

to which the petition was filed as the Secretary may require;

(iii) information to show that the route of administration, the dosage form, and the strength of the new drug are the same as those of the listed drug referred to in clause (i) or, if the route of administration, the dosage form, or the strength of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), such information respecting the route of administration, dosage form, or strength with respect to which the petition was filed as the Secretary may require;

(iv) information to show that the new drug is bioequivalent to the listed drug referred to in clause (i), except that if the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in clause (i) and the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in clause (i);

(v) information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers;

(vi) the items specified in clauses (B) through (F) of subsection (b)(1) of this section;

(vii) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the listed drug referred to in clause (i) or which claims a use for such listed drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (c) of this section—

(I) that such patent information has not been filed,

(II) that such patent has expired,

(III) of the date on which such patent will expire, or

(IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(viii) if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).

(B) Notice of opinion that patent is invalid or will not be infringed

(i) Agreement to give notice—An applicant that makes a certification described in subparagraph (A)(vii)(IV) shall include in the application a statement that the applicant will give notice as required by this subparagraph.

(ii) Timing of notice—An applicant that makes a certification described in subparagraph (A)(vii)(IV) shall give notice as required under this subparagraph—

(I) if the certification is in the application, not later than 20 days after the date of the postmark on the notice with which the Secretary informs the applicant that the application has been filed; or

(III) if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.

(iii) Recipients of notice—An applicant required under this subparagraph to give notice shall give notice to—

(I) each owner of the patent that is the subject of the certification (or a representative of the owner designated to receive such a notice); and

(II) the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent (or a representative of the holder designated to receive such a notice).

(iv) Contents of notice—A notice required under this subparagraph shall—

(I) state that an application that contains data from bioavailability or bioequivalence studies has been submitted under this subsection for the drug with respect

to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification; and

(II) include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.

(C) If a person wants to submit an abbreviated application for a new drug which has a different active ingredient or whose route of administration, dosage form, or strength differ from that of a listed drug, such person shall submit a petition to the Secretary seeking permission to file such an application. The Secretary shall approve or disapprove a petition submitted under this subparagraph within ninety days of the date the petition is submitted. The Secretary shall approve such a petition unless the Secretary finds—

(i) that investigations must be conducted to show the safety and effectiveness of the drug or of any of its active ingredients, the route of administration, the dosage form, or strength which differ from the listed drug; or

(ii) that any drug with a different active ingredient may not be adequately evaluated for approval as safe and ef-

fective on the basis of the information required to be submitted in an abbreviated application.

(D)(i) An applicant may not amend or supplement an application to seek approval of a drug referring to a different listed drug from the listed drug identified in the application as submitted to the Secretary.

(ii) With respect to the drug for which an application is submitted, nothing in this subsection prohibits an applicant from amending or supplementing the application to seek approval of a different strength.

(iii) Within 60 days after December 8, 2003, the Secretary shall issue guidance defining the term "listed drug" for purposes of this subparagraph.

(3)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1), which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection if the sponsor or applicant makes a reasonable written request for a meeting for

the purpose of reaching agreement on the design and size of bioavailability and bioequivalence studies needed for approval of such application. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of such studies. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant.

(C) Any agreement regarding the parameters of design and size of bioavailability and bioequivalence studies of a drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except—

(i) with the written agreement of the sponsor or applicant; or

(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the

director will document the scientific issue involved.

(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance office personnel unless such field or compliance office personnel demonstrate to the reviewing division why such decision should be modified.

(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection (including scientific matters, chemistry, manufacturing, and controls).

(4) Subject to paragraph (5), the Secretary shall approve an application for a drug unless the Secretary finds—

(A) the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity;

(B) information submitted with the application is insufficient to show that each of

the proposed conditions of use have been previously approved for the listed drug referred to in the application;

(C)(i) if the listed drug has only one active ingredient, information submitted with the application is insufficient to show that the active ingredient is the same as that of the listed drug;

(ii) if the listed drug has more than one active ingredient, information submitted with the application is insufficient to show that the active ingredients are the same as the active ingredients of the listed drug, or

(iii) if the listed drug has more than one active ingredient and if the application is for a drug which has an active ingredient different from the listed drug, information submitted with the application is insufficient to show—

(I) that the other active ingredients are the same as the active ingredients of the listed drug, or

(II) that the different active ingredient is an active ingredient of a listed drug or a drug which does not meet the requirements of section 321(p) of this title, or no petition to file an application for the drug with the different ingredient was approved under paragraph (2)(C);

(D)(i) if the application is for a drug whose route of administration, dosage form, or strength of the drug is the same as the route of administration, dosage form, or strength of the listed drug referred to in the application, information submitted in the application is insufficient to show that the route of administration, dosage form, or strength is the same as that of the listed drug, or

(ii) if the application is for a drug whose route of administration, dosage form, or strength of the drug is different from that of the listed drug referred to in the application, no petition to file an application for the drug with the different route of administration, dosage form, or strength was approved under paragraph (2)(C);

(E) if the application was filed pursuant to the approval of a petition under paragraph (2)(C), the application did not contain the information required by the Secretary respecting the active ingredient, route of administration, dosage form, or strength which is not the same;

(F) information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug referred to in the application or, if the application was filed pursuant to a petition approved under paragraph (2)(C), information submitted in the application is insuffi-

cient to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in paragraph (2)(A)(i) and that the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in such paragraph;

(G) information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the application except for changes required because of differences approved under a petition filed under paragraph (2)(C) or because the drug and the listed drug are produced or distributed by different manufacturers;

(H) information submitted in the application or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included;

(I) the approval under subsection (c) of this section of the listed drug referred to in the application under this subsection has

been withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section, the Secretary has published a notice of opportunity for hearing to withdraw approval of the listed drug under subsection (c) of this section for grounds described in the first sentence of subsection (e) of this section, the approval under this subsection of the listed drug referred to in the application under this subsection has been withdrawn or suspended under paragraph (6), or the Secretary has determined that the listed drug has been withdrawn from sale for safety or effectiveness reasons;

(J) the application does not meet any other requirement of paragraph (2)(A); or

(K) the application contains an untrue statement of material fact.

(5)(A) Within one hundred and eighty days of the initial receipt of an application under paragraph (2) or within such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall approve or disapprove the application.

(B) The approval of an application submitted under paragraph (2) shall be made effective on the last applicable date determined by applying the following to each certification made under paragraph (2)(A)(vii):

(i) If the applicant only made a certification described in subclause (I) or (II)

of paragraph (2)(A)(vii) or in both such subclauses, the approval may be made effective immediately.

(ii) If the applicant made a certification described in subclause (III) of paragraph (2)(A)(vii), the approval may be made effective on the date certified under subclause (III).

(iii) If the applicant made a certification described in subclause (IV) of paragraph (2)(A)(vii), the approval shall be made effective immediately unless, before the expiration of 45 days after the date on which the notice described in paragraph (2)(B) is received, an action is brought for infringement of the patent that is the subject of the certification and for which information was submitted to the Secretary under subsection (b)(1) or (c)(2) of this section before the date on which the application (excluding an amendment or supplement to the application), which the Secretary later determines to be substantially complete, was submitted. If such an action is brought before the expiration of such days, the approval shall be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under paragraph (2)(B)(i) or such shorter or longer period as the court may order because either party to the action failed to reasonably coo-

perate in expediting the action, except that—

(I) if before the expiration of such period the district court decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the approval shall be made effective on—

(aa) the date on which the court enters judgment reflecting the decision; or

(bb) the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed;

(II) if before the expiration of such period the district court decides that the patent has been infringed—

(aa) if the judgment of the district court is appealed, the approval shall be made effective on—the

(AA) the date on which the court of appeals decides that the patent is invalid or not infringed (including any substantive de-

termination that there is no cause of action for patent infringement or invalidity); or

(BB) the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid or not infringed; or

(bb) if the judgment of the district court is not appealed or is affirmed, the approval shall be made effective on the date specified by the district court in a court order under section 271(e)(4)(A) of Title 35;

(III) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective as provided in subclause (I); or

(IV) if before the expiration of such period the court grants a preliminary injunction prohibiting the

applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent has been infringed, the approval shall be made effective as provided in subclause (II).

In such an action, each of the parties shall reasonably cooperate in expediting the action.

(iv) 180-day exclusivity period

(I) Effectiveness of application—Subject to subparagraph (D), if the application contains a certification described in paragraph (2)(A)(vii)(IV) and is for a drug for which a first applicant has submitted an application containing such a certification, the application shall be made effective on the date that is 180 days after the date of the first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant.

(II) Definitions—In this paragraph:

(aa) 180-day exclusivity period—The term "180-day exclusivity period" means the 180-day period ending on the day before the date on which an application submitted by an ap-

plicant other than a first applicant could become effective under this clause.

(bb) First applicant—As used in this subsection, the term "first applicant" means an applicant that, on the first day on which a substantially complete application containing a certification described in paragraph (2)(A)(vii)(IV) is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a certification described in paragraph (2)(A)(vii)(IV) for the drug.

(cc) Substantially complete application—As used in this subsection, the term "substantially complete application" means an application under this subsection that on its face is sufficiently complete to permit a substantive review and contains all the information required by paragraph (2)(A).

(dd) Tentative approval

(AA) In general—The term "tentative approval" means notification to an applicant by the Secre-

tary that an application under this subsection meets the requirements of paragraph (2)(A), but cannot receive effective approval because the application does not meet the requirements of this subparagraph, there is a period of exclusivity for the listed drug under subparagraph (F) or section 355a of this title, or there is a 7-year period of exclusivity for the listed drug under section 360cc of this title.

(BB) Limitation—A drug that is granted tentative approval by the Secretary is not an approved drug and shall not have an effective approval until the Secretary issues an approval after any necessary additional review of the application.

(C) Civil action to obtain patent certainty

(i) Declaratory judgment absent infringement action

(I) In general—No action may be brought under section 2201 of Title 28, by an applicant under paragraph (2) for a declaratory

judgment with respect to a patent which is the subject of the certification referred to in subparagraph (B)(iii) unless—

(aa) the 45-day period referred to in such subparagraph has expired;

(bb) neither the owner of such patent nor the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brought a civil action against the applicant for infringement of the patent before the expiration of such period; and

(cc) in any case in which the notice provided under paragraph (2)(B) relates to noninfringement, the notice was accompanied by a document described in subclause (III).

(II) Filing of civil action—If the conditions described in items (aa), (bb), and as applicable, (cc) of subclause (I) have been met, the applicant referred to in such subclause may, in accordance with section 2201 of Title 28, bring a civil action under such section against the owner or holder referred to in such subclause (but

not against any owner or holder that has brought such a civil action against the applicant, unless that civil action was dismissed without prejudice) for a declaratory judgment that the patent is invalid or will not be infringed by the drug for which the applicant seeks approval, except that such civil action may be brought for a declaratory judgment that the patent will not be infringed only in a case in which the condition described in subclause (I)(cc) is applicable. A civil action referred to in this subclause shall be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

(III) Offer of confidential access to application—For purposes of subclause (I)(cc), the document described in this subclause is a document providing an offer of confidential access to the application that is in the custody of the applicant under paragraph (2) for the purpose of determining whether an action referred to in subparagraph (B)(iii) should be brought. The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the

use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV) and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no

relevance to any issue of patent infringement.

(ii) Counterclaim to infringement action

(I) In general—If an owner of the patent or the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) of this section on the ground that the patent does not claim either—

(aa) the drug for which the application was approved; or

(bb) an approved method of using the drug.

(II) No independent cause of action—Subclause (I) does not authorize the assertion of a claim described in subclause (I) in any civil action or proceeding other than a counterclaim described in subclause (I).

(iii) No damages—An applicant shall not be entitled to damages in a civil ac-

tion under clause (i) or a counterclaim under clause (ii).

(D) Forfeiture of 180-day exclusivity period

(i) Definition of forfeiture event—In this subparagraph, the term "forfeiture event", with respect to an application under this subsection, means the occurrence of any of the following:

(I) Failure to market –The first applicant fails to market the drug by the later of—

(aa) the earlier of the date that is—

(AA) 75 days after the date on which the approval of the application of the first applicant is made effective under subparagraph (B)(iii); or

(BB) 30 months after the date of submission of the application of the first applicant; or

(bb) with respect to the first applicant or any other applicant (which other applicant has received tentative approval), the date that is 75 days after the date as of which, as to each of the patents with respect to which the first applicant submitted and lawfully maintained a certification

qualifying the first applicant for the 180-day exclusivity period under subparagraph (B)(iv), at least 1 of the following has occurred:

(AA) In an infringement action brought against that applicant with respect to the patent or in a declaratory judgment action brought by that applicant with respect to the patent, a court enters a final decision from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the patent is invalid or not infringed.

(BB) In an infringement action or a declaratory judgment action described in subitem (AA), a court signs a settlement order or consent decree that enters a final judgment that includes a finding that the patent is invalid or not infringed.

(CC) The patent information submitted under subsection (b) or (c) of this section is withdrawn by the

holder of the application approved under subsection (b) of this section.

(II) Withdrawal of application—The first applicant withdraws the application or the Secretary considers the application to have been withdrawn as a result of a determination by the Secretary that the application does not meet the requirements for approval under paragraph (4).

(III) Amendment of certification—The first applicant amends or withdraws the certification for all of the patents with respect to which that applicant submitted a certification qualifying the applicant for the 180-day exclusivity period.

(IV) Failure to obtain tentative approval—The first applicant fails to obtain tentative approval of the application within 30 months after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed.

(V) Agreement with another applicant, the listed drug application holder, or a patent owner—The first applicant enters into an

agreement with another applicant under this subsection for the drug, the holder of the application for the listed drug, or an owner of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV), the Federal Trade Commission or the Attorney General files a complaint, and there is a final decision of the Federal Trade Commission or the court with regard to the complaint from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the agreement has violated the antitrust laws (as defined in section 12 of Title 15, except that the term includes section 45 of Title 15 to the extent that that section applies to unfair methods of competition).

(VI) Expiration of all patents—All of the patents as to which the applicant submitted a certification qualifying it for the 180-day exclusivity period have expired.

(ii) Forfeiture—The 180-day exclusivity period described in subparagraph (B)(iv) shall be forfeited by a first applicant if a forfeiture event occurs with respect to that first applicant.

(iii) Subsequent applicant—If all first applicants forfeit the 180-day exclusivity period under clause (ii)—

(I) approval of any application containing a certification described in paragraph (2)(A)(vii)(IV) shall be made effective in accordance with subparagraph (B)(iii); and

(II) no applicant shall be eligible for a 180-day exclusivity period.

(E) If the Secretary decides to disapprove an application, the Secretary shall give the applicant notice of an opportunity for a hearing before the Secretary on the question of whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(F)(i) If an application (other than an abbreviated new drug application) submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other applica-

tion under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted effective before the expiration of ten years from the date of the approval of the application under subsection (b) of this section.

(ii) If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b) of this section, except that such an application may be submitted under this subsection after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in subclause (IV) of paragraph (2)(A)(vii). The ap-

proval of such an application shall be made effective in accordance with subparagraph (B) except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (B)(iii) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date

of the approval of the application under subsection (b) of this section for such drug.

(iv) If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section.

(v) If an application (or supplement to an application) submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was sub-

mitted or which refers to a change approved in a supplement to the subsection (b) application effective before the expiration of two years from September 24, 1984.

(6) If a drug approved under this subsection refers in its approved application to a drug the approval of which was withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section or was withdrawn or suspended under this paragraph or which, as determined by the Secretary, has been withdrawn from sale for safety or effectiveness reasons, the approval of the drug under this subsection shall be withdrawn or suspended—

(A) for the same period as the withdrawal or suspension under subsection (e) of this section or this paragraph, or

(B) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

(7)(A)(i) Within sixty days of September 24, 1984, the Secretary shall publish and make available to the public--

(I) a list in alphabetical order of the official and proprietary name of each drug which has been approved for safety and effectiveness under subsection (c) of this

section before September 24, 1984;

(II) the date of approval if the drug is approved after 1981 and the number of the application which was approved; and

(III) whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications filed under this subsection which will refer to the drug published.

(ii) Every thirty days after the publication of the first list under clause (i) the Secretary shall revise the list to include each drug which has been approved for safety and effectiveness under subsection (c) of this section or approved under this subsection during the thirty-day period.

(iii) When patent information submitted under subsection (b) or (c) of this section respecting a drug included on the list is to be published by the Secretary, the Secretary shall, in revisions made under clause (ii), include such information for such drug.

(B) A drug approved for safety and effectiveness under subsection (c) of this section or approved under this subsection shall, for purposes of this subsection, be considered to have been published under subparagraph (A) on the date of its approval

or September 24, 1984, whichever is later.

(C) If the approval of a drug was withdrawn or suspended for grounds described in the first sentence of subsection (e) of this section or was withdrawn or suspended under paragraph (6) or if the Secretary determines that a drug has been withdrawn from sale for safety or effectiveness reasons, it may not be published in the list under subparagraph (A) or, if the withdrawal or suspension occurred after its publication in such list, it shall be immediately removed from such list—

(i) for the same period as the withdrawal or suspension under subsection (e) of this section or paragraph (6), or

(ii) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

A notice of the removal shall be published in the Federal Register.

(8) For purposes of this subsection:

(A)(i) The term "bioavailability" means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.

(ii) For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action.

(B) A drug shall be considered to be bioequivalent to a listed drug if—

(i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or

(ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

(C) For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

(9) The Secretary shall, with respect to each application submitted under this subsection, maintain a record of—

(A) the name of the applicant,

(B) the name of the drug covered by the application,

(C) the name of each person to whom the review of the chemistry of the application was assigned and the date of such assignment, and

(D) the name of each person to whom the bioequivalence review for such application was assigned and the date of such assignment.

The information the Secretary is required to maintain under this paragraph with respect to an application submitted under this subsection shall be made available to the public after the approval of such application.

(10)(A) If the proposed labeling of a drug that is the subject of an application under this subsection differs from the listed drug due to a labeling revision described under clause (i), the drug that is the subject of such application shall, notwithstanding

any other provision of this chapter, be eligible for approval and shall not be considered misbranded under section 352 of this title if—

(i) the application is otherwise eligible for approval under this subsection but for expiration of patent, an exclusivity period, or of a delay in approval described in paragraph (5)(B)(iii), and a revision to the labeling of the listed drug has been approved by the Secretary within 60 days of such expiration;

(ii) the labeling revision described under clause (i) does not include a change to the "Warnings" section of the labeling;

(iii) the sponsor of the application under this subsection agrees to submit revised labeling of the drug that is the subject of such application not later than 60 days after the notification of any changes to such labeling required by the Secretary; and

(iv) such application otherwise meets the applicable requirements for approval under this subsection.

(B) If, after a labeling revision described in subparagraph (A)(i), the Secretary determines that the continued presence in interstate commerce of the labeling of the listed drug (as in effect before the revision described in subparagraph (A)(i)) adversely impacts the safe use of the

drug, no application under this subsection shall be eligible for approval with such labeling.

(k) Records and reports; required information; regulations and orders; access to records

(1) In the case of any drug for which an approval of an application filed under subsection (b) or (j) of this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section. Regulations and orders issued under this subsection and under subsection (i) of this section shall have due regard for the professional ethics of the medical profession and the interests of patients and shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulations or orders are applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this section to maintain records, and every person in charge or custody thereof, shall, upon request of an

officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

(3) Active postmarket risk identification

(A) Definition—In this paragraph, the term "data" refers to information with respect to a drug approved under this section or under section 262 of Title 42, including claims data, patient survey data, standardized analytic files that allow for the pooling and analysis of data from disparate data environments, and any other data deemed appropriate by the Secretary.

(B) Development of postmarket risk identification and analysis methods—The Secretary shall, not later than 2 years after September 27, 2007, in collaboration with public, academic, and private entities—

(i) develop methods to obtain access to disparate data sources including the data sources specified in subparagraph (C);

(ii) develop validated methods for the establishment of a postmarket risk identification and analysis system to link and analyze safety data from multiple sources, with the goals of including, in aggregate—

(I) at least 25,000,000 patients by July 1, 2010; and

(II) at least 100,000,000 patients by July 1, 2012; and

(iii) convene a committee of experts, including individuals who are recognized in the field of protecting data privacy and security, to make recommendations to the Secretary on the development of tools and methods for the ethical and scientific uses for, and communication of, postmarketing data specified under subparagraph (C), including recommendations on the development of effective research methods for the study of drug safety questions.

(C) Establishment of the postmarket risk identification and analysis system

(i) In general—The Secretary shall, not later than 1 year after the development of the risk identification and analysis methods under subparagraph (B), establish and maintain procedures—

(I) for risk identification and analysis based on electronic health data, in compliance with the regulations promulgated under section 264(c) of the Health Insurance Portability and Accountability Act of 1996, and in a manner that does not disclose individually identifiable health information in violation of paragraph (4)(B);

(II) for the reporting (in a standardized form) of data on all serious adverse drug experiences (as defined in section 355-1(b) of this title) submitted to the Secretary under paragraph (1), and those adverse events submitted by patients, providers, and drug sponsors, when appropriate;

(III) to provide for active adverse event surveillance using the following data sources, as available:

(aa) Federal health-related electronic data (such as data from the Medicare program and the health systems of the Department of Veterans Affairs);

(bb) private sector health-related electronic data (such as pharmaceutical purchase data and health insurance claims data); and

(cc) other data as the Secretary deems necessary to create a robust system to identify adverse events and potential drug safety signals;

(IV) to identify certain trends and patterns with respect to data accessed by the system;

(V) to provide regular reports to the Secretary concerning adverse

event trends, adverse event patterns, incidence and prevalence of adverse events, and other information the Secretary determines appropriate, which may include data on comparative national adverse event trends; and

(VI) to enable the program to export data in a form appropriate for further aggregation, statistical analysis, and reporting.

(ii) Timeliness of reporting—The procedures established under clause (i) shall ensure that such data are accessed, analyzed, and reported in a timely, routine, and systematic manner, taking into consideration the need for data completeness, coding, cleansing, and standardized analysis and transmission.

(iii) Private sector resources—To ensure the establishment of the active postmarket risk identification and analysis system under this subsection not later than 1 year after the development of the risk identification and analysis methods under subparagraph (B), as required under clause (i), the Secretary may, on a temporary or permanent basis, implement systems or products developed by private entities.

(iv) Complementary approaches—To the extent the active postmarket risk

identification and analysis system under this subsection is not sufficient to gather data and information relevant to a priority drug safety question, the Secretary shall develop, support, and participate in complementary approaches to gather and analyze such data and information, including—

(I) approaches that are complementary with respect to assessing the safety of use of a drug in domestic populations not included, or underrepresented, in the trials used to approve the drug (such as older people, people with comorbidities, pregnant women, or children); and

(II) existing approaches such as the Vaccine Adverse Event Reporting System and the Vaccine Safety Datalink or successor databases.

(v) Authority for contracts—The Secretary may enter into contracts with public and private entities to fulfill the requirements of this subparagraph.

(4) Advanced analysis of drug safety data

(A) Purpose—The Secretary shall establish collaborations with public, academic, and private entities, which may include the Centers for Education and Research on Therapeutics under section 299b-1 of Title 42, to provide for advanced analysis

of drug safety data described in paragraph (3)(C) and other information that is publicly available or is provided by the Secretary, in order to—

(i) improve the quality and efficiency of postmarket drug safety risk-benefit analysis;

(ii) provide the Secretary with routine access to outside expertise to study advanced drug safety questions; and

(iii) enhance the ability of the Secretary to make timely assessments based on drug safety data.

(B) Privacy—Such analysis shall not disclose individually identifiable health information when presenting such drug safety signals and trends or when responding to inquiries regarding such drug safety signals and trends.

(C) Public process for priority questions—At least biannually, the Secretary shall seek recommendations from the Drug Safety and Risk Management Advisory Committee (or any successor committee) and from other advisory committees, as appropriate, to the Food and Drug Administration on—

(i) priority drug safety questions; and

(ii) mechanisms for answering such questions, including through—

(I) active risk identification under paragraph (3); and

(III) when such risk identification is not sufficient, postapproval studies and clinical trials under subsection (o)(3) of this section.

(D) Procedures for the development of drug safety collaborations

(i) In general—Not later than 180 days after the date of the establishment of the active postmarket risk identification and analysis system under this subsection, the Secretary shall establish and implement procedures under which the Secretary may routinely contract with one or more qualified entities to—

(I) classify, analyze, or aggregate data described in paragraph (3)(C) and information that is publicly available or is provided by the Secretary;

(II) allow for prompt investigation of priority drug safety questions, including—

(aa) unresolved safety questions for drugs or classes of drugs; and

(bb) for a newly-approved drugs, safety signals from clinical trials used to approve the drug and other preapproval trials; rare, serious drug side effects; and the safety of use in domestic populations not

included, or underrepresented, in the trials used to approve the drug (such as older people, people with comorbidities, pregnant women, or children);

(III) perform advanced research and analysis on identified drug safety risks;

(IV) focus postapproval studies and clinical trials under subsection (o)(3) of this section more effectively on cases for which reports under paragraph (1) and other safety signal detection is not sufficient to resolve whether there is an elevated risk of a serious adverse event associated with the use of a drug; and

(V) carry out other activities as the Secretary deems necessary to carry out the purposes of this paragraph.

(ii) Request for specific methodology—The procedures described in clause (i) shall permit the Secretary to request that a specific methodology be used by the qualified entity. The qualified entity shall work with the Secretary to finalize the methodology to be used.

(E) Use of analyses—The Secretary shall provide the analyses described in this paragraph, including the methods and re-

sults of such analyses, about a drug to the sponsor or sponsors of such drug.

(F) Qualified entities

(i) In general—The Secretary shall enter into contracts with a sufficient number of qualified entities to develop and provide information to the Secretary in a timely manner.

(ii) Qualification—The Secretary shall enter into a contract with an entity under clause (i) only if the Secretary determines that the entity has a significant presence in the United States and has one or more of the following qualifications:

(I) The research, statistical, epidemiologic, or clinical capability and expertise to conduct and complete the activities under this paragraph, including the capability and expertise to provide the Secretary de-identified data consistent with the requirements of this subsection.

(II) An information technology infrastructure in place to support electronic data and operational standards to provide security for such data.

(III) Experience with, and expertise on, the development of drug safety and effectiveness research using electronic population data.

(IV) An understanding of drug development or risk/benefit balancing in a clinical setting.

(V) Other expertise which the Secretary deems necessary to fulfill the activities under this paragraph.

(G) Contract requirements—Each contract with a qualified entity under subparagraph (F)(i) shall contain the following requirements:

(i) Ensuring privacy—The qualified entity shall ensure that the entity will not use data under this subsection in a manner that—

(I) violates the regulations promulgated under section 264(c) of the Health Insurance Portability and Accountability Act of 1996;

(II) violates sections 552 or 552a of Title 5 with regard to the privacy of individually-identifiable beneficiary health information; or

(III) discloses individually identifiable health information when presenting drug safety signals and trends or when responding to inquiries regarding drug safety signals and trends.

Nothing in this clause prohibits lawful disclosure for other purposes.

(ii) Component of another organization—If a qualified entity is a component of another organization—

(I) the qualified entity shall establish appropriate security measures to maintain the confidentiality and privacy of such data; and

(II) the entity shall not make an unauthorized disclosure of such data to the other components of the organization in breach of such confidentiality and privacy requirement.

(iii) Termination or nonrenewal—If a contract with a qualified entity under this subparagraph is terminated or not renewed, the following requirements shall apply:

(I) Confidentiality and privacy protections—The entity shall continue to comply with the confidentiality and privacy requirements under this paragraph with respect to all data disclosed to the entity.

(II) Disposition of data—The entity shall return any data disclosed to such entity under this subsection to which it would not otherwise have access or, if returning the data is not practicable, destroy the data.

(H) Competitive procedures—The Secretary shall use competitive procedures (as defined in section 403(5) of Title 41) to enter into contracts under subparagraph (G).

(I) Review of contract in the event of a merger or acquisition—The Secretary shall review the contract with a qualified entity under this paragraph in the event of a merger or acquisition of the entity in order to ensure that the requirements under this paragraph will continue to be met.

(J) Coordination—In carrying out this paragraph, the Secretary shall provide for appropriate communications to the public, scientific, public health, and medical communities, and other key stakeholders, and to the extent practicable shall coordinate with the activities of private entities, professional associations, or other entities that may have sources of drug safety data.

(5) The Secretary shall—

(A) conduct regular, bi-weekly screening of the Adverse Event Reporting System database and post a quarterly report on the Adverse Event Reporting System Web site of any new safety information or potential signal of a serious risk identified by Adverse Event Reporting System within the last quarter;

(B) report to Congress not later than 2 year[2] after September 27, 2007 on procedures and processes of the Food and Drug Administration for addressing ongoing post market safety issues identified by the Office of Surveillance and Epidemiology and how recommendations of the Office of Surveillance and Epidemiology are handled within the agency; and

(C) on an annual basis, review the entire backlog of postmarket safety commitments to determine which commitments require revision or should be eliminated, report to the Congress on these determinations, and assign start dates and estimated completion dates for such commitments.

(l) Public disclosure of safety and effectiveness data

(1) Safety and effectiveness data and information which has been submitted in an application under subsection (b) of this section for a drug and which has not previously been disclosed to the public shall be made available to the public, upon request, unless extraordinary circumstances are shown—

(A) if no work is being or will be undertaken to have the application approved,

(B) if the Secretary has determined that the application is not approvable and all legal appeals have been exhausted,

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[2] So in original. Probably should be "years".

(C) if approval of the application under subsection (c) of this section is withdrawn and all legal appeals have been exhausted,

(D) if the Secretary has determined that such drug is not a new drug, or

(E) upon the effective date of the approval of the first application under subsection (j) of this section which refers to such drug or upon the date upon which the approval of an application under subsection (j) of this section which refers to such drug could be made effective if such an application had been submitted.

(2) Action package for approval

(A) Action package—The Secretary shall publish the action package for approval of an application under subsection (b) of this section or section 262 of title 42 on the Internet Web site of the Food and Drug Administration—

(i) not later than 30 days after the date of approval of such application for a drug no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under this section or section 262 of Title 42; and

(ii) not later than 30 days after the third request for such action package for approval received under section 552 of Title 5 for any other drug.

(B) Immediate publication of summary review—Notwithstanding subparagraph (A), the Secretary shall publish, on the Internet Web site of the Food and Drug Administration, the materials described in subparagraph (C)(iv) not later than 48 hours after the date of approval of the drug, except where such materials require redaction by the Secretary.

(C) Contents—An action package for approval of an application under subparagraph (A) shall be dated and shall include the following:

(i) Documents generated by the Food and Drug Administration related to review of the application.

(ii) Documents pertaining to the format and content of the application generated during drug development.

(iii) Labeling submitted by the applicant.

(iv) A summary review that documents conclusions from all reviewing disciplines about the drug, noting any critical issues and disagreements with the applicant and within the review team and how they were resolved, recommendations for action, and an explanation of any nonconcurrence with review conclusions.

(v) The Division Director and Office Director's decision document which includes—

(I) a brief statement of concurrence with the summary review;

(II) a separate review or addendum to the review if disagreeing with the summary review; and

(III) a separate review or addendum to the review to add further analysis.

(vi) Identification by name of each officer or employee of the Food and Drug Administration who—

(I) participated in the decision to approve the application; and

(II) consents to have his or her name included in the package.

(D) Review—A scientific review of an application is considered the work of the reviewer and shall not be altered by management or the reviewer once final.

(E) Confidential information—This paragraph does not authorize the disclosure of any trade secret, confidential commercial or financial information, or other matter listed in section 552(b) of Title 5.

(m) "Patent" defined

For purposes of this section, the term "patent" means a patent issued by the United States Patent and Trademark Office.

(n) Scientific advisory panels

(1) For the purpose of providing expert scientific advice and recommendations to the Secretary

regarding a clinical investigation of a drug or the approval for marketing of a drug under this section or section 262 of Title 42, the Secretary shall establish panels of experts or use panels of experts established before November 21, 1997, or both.

(2) The Secretary may delegate the appointment and oversight authority granted under section 394 of this title to a director of a center or successor entity within the Food and Drug Administration.

(3) The Secretary shall make appointments to each panel established under paragraph (1) so that each panel shall consist of—

(A) members who are qualified by training and experience to evaluate the safety and effectiveness of the drugs to be referred to the panel and who, to the extent feasible, possess skill and experience in the development, manufacture, or utilization of such drugs;

(B) members with diverse expertise in such fields as clinical and administrative medicine, pharmacy, pharmacology, pharmacoeconomics, biological and physical sciences, and other related professions;

(C) a representative of consumer interests, and a representative of interests of the drug manufacturing industry not directly affected by the matter to be brought before the panel; and

(D) two or more members who are specialists or have other expertise in the particular

disease or condition for which the drug under review is proposed to be indicated.

Scientific, trade, and consumer organizations shall be afforded an opportunity to nominate individuals for appointment to the panels. No individual who is in the regular full-time employ of the United States and engaged in the administration of this chapter may be a voting member of any panel. The Secretary shall designate one of the members of each panel to serve as chairman thereof.

(4) The Secretary shall, as appropriate, provide education and training to each new panel member before such member participates in a panel's activities, including education regarding requirements under this chapter and related regulations of the Secretary, and the administrative processes and procedures related to panel meetings.

(5) Panel members (other than officers or employees of the United States), while attending meetings or conferences of a panel or otherwise engaged in its business, shall be entitled to receive compensation for each day so engaged, including traveltime, at rates to be fixed by the Secretary, but not to exceed the daily equivalent of the rate in effect for positions classified above grade GS-15 of the General Schedule. While serving away from their homes or regular places of business, panel members may be allowed travel expenses (including per diem in lieu of subsistence) as authorized by section 5703 of Title 5, for persons in the Government service employed intermittently.

(6) The Secretary shall ensure that scientific advisory panels meet regularly and at appropriate intervals so that any matter to be reviewed by such a panel can be presented to the panel not more than 60 days after the matter is ready for such review. Meetings of the panel may be held using electronic communication to convene the meetings.

(7) Within 90 days after a scientific advisory panel makes recommendations on any matter under its review, the Food and Drug Administration official responsible for the matter shall review the conclusions and recommendations of the panel, and notify the affected persons of the final decision on the matter, or of the reasons that no such decision has been reached. Each such final decision shall be documented including the rationale for the decision.

(8) Redesignated (7)

(o) Postmarket studies and clinical trials; labeling

(1) In general—A responsible person may not introduce or deliver for introduction into interstate commerce the new drug involved if the person is in violation of a requirement established under paragraph (3) or (4) with respect to the drug.

(2) Definitions—For purposes of this subsection:

(A) Responsible person—The term "responsible person" means a person who—

(i) has submitted to the Secretary a covered application that is pending; or

(ii) is the holder of an approved covered application.

(B) Covered application—The term "covered application" means—

(i) an application under subsection (b) of this section for a drug that is subject to section 353(b) of this title; and

(ii) an application under section 262 of Title 42.

(C) New safety information; serious risk—The terms "new safety information", "serious risk", and "signal of a serious risk" have the meanings given such terms in section 355-1(b) of this title.

(3) Studies and clinical trials

(A) In general—For any or all of the purposes specified in subparagraph (B), the Secretary may, subject to subparagraph (D), require a responsible person for a drug to conduct a postapproval study or studies of the drug, or a postapproval clinical trial or trials of the drug, on the basis of scientific data deemed appropriate by the Secretary, including information regarding chemically-related or pharmacologically-related drugs.

(B) Purposes of study or clinical trial—The purposes referred to in this subparagraph with respect to a postapproval study or postapproval clinical trial are the following:

(i) To assess a known serious risk related to the use of the drug involved.

(ii) To assess signals of serious risk related to the use of the drug.

(iii) To identify an unexpected serious risk when available data indicates the potential for a serious risk.

(C) Establishment of requirement after approval of covered application—The Secretary may require a postapproval study or studies or postapproval clinical trial or trials for a drug for which an approved covered application is in effect as of the date on which the Secretary seeks to establish such requirement only if the Secretary becomes aware of new safety information.

(D) Determination by Secretary

(i) Postapproval studies—The Secretary may not require the responsible person to conduct a study under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) of this section and the active postmarket risk identification and analysis system as available under subsection (k)(3) of this section will not be sufficient to meet the purposes set forth in subparagraph (B).

(ii) Postapproval clinical trials—The Secretary may not require the responsible person to conduct a clinical trial

under this paragraph, unless the Secretary makes a determination that a postapproval study or studies will not be sufficient to meet the purposes set forth in subparagraph (B).

(E) Notification; timetables; periodic reports

(i) Notification—The Secretary shall notify the responsible person regarding a requirement under this paragraph to conduct a postapproval study or clinical trial by the target dates for communication of feedback from the review team to the responsible person regarding proposed labeling and postmarketing study commitments as set forth in the letters described in section 101(c) of the Food and Drug Administration Amendments Act of 2007.

(ii) Timetable; periodic reports—For each study or clinical trial required to be conducted under this paragraph, the Secretary shall require that the responsible person submit a timetable for completion of the study or clinical trial. With respect to each study required to be conducted under this paragraph or otherwise undertaken by the responsible person to investigate a safety issue, the Secretary shall require the responsible person to periodically report to the Secretary on the status of such study including whether any difficulties in completing

the study have been encountered. With respect to each clinical trial required to be conducted under this paragraph or otherwise undertaken by the responsible person to investigate a safety issue, the Secretary shall require the responsible person to periodically report to the Secretary on the status of such clinical trial including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to the requirements under section 282(j) of Title 42. If the responsible person fails to comply with such timetable or violates any other requirement of this subparagraph, the responsible person shall be considered in violation of this subsection, unless the responsible person demonstrates good cause for such noncompliance or such other violation. The Secretary shall determine what constitutes good cause under the preceding sentence.

(F) Dispute resolution—The responsible person may appeal a requirement to conduct a study or clinical trial under this paragraph using dispute resolution procedures established by the Secretary in regulation and guidance.

(4) Safety labeling changes requested by Secretary

(A) New safety information—If the Secretary becomes aware of new safety information that the Secretary believes should be included in the labeling of the drug, the Secretary shall promptly notify the responsible person or, if the same drug approved under subsection (b) of this section is not currently marketed, the holder of an approved application under subsection (j) of this section.

(B) Response to notification—Following notification pursuant to subparagraph (A), the responsible person or the holder of the approved application under subsection (j) of this section shall within 30 days—

(i) submit a supplement proposing changes to the approved labeling to reflect the new safety information, including changes to boxed warnings, contraindications, warnings, precautions, or adverse reactions; or

(ii) notify the Secretary that the responsible person or the holder of the approved application under subsection (j) of this section does not believe a labeling change is warranted and submit a statement detailing the reasons why such a change is not warranted.

(C) Review—Upon receipt of such supplement, the Secretary shall promptly re-

view and act upon such supplement. If the Secretary disagrees with the proposed changes in the supplement or with the statement setting forth the reasons why no labeling change is necessary, the Secretary shall initiate discussions to reach agreement on whether the labeling for the drug should be modified to reflect the new safety information, and if so, the contents of such labeling changes.

(D) Discussions—Such discussions shall not extend for more than 30 days after the response to the notification under subparagraph (B), unless the Secretary determines an extension of such discussion period is warranted.

(E) Order—Within 15 days of the conclusion of the discussions under subparagraph (D), the Secretary may issue an order directing the responsible person or the holder of the approved application under subsection (j) of this section to make such a labeling change as the Secretary deems appropriate to address the new safety information. Within 15 days of such an order, the responsible person or the holder of the approved application under subsection (j) of this section shall submit a supplement containing the labeling change.

(F) Dispute resolution—Within 5 days of receiving an order under subparagraph (E), the responsible person or the holder of the approved application under subsection (j) of this section may appeal using

dispute resolution procedures established by the Secretary in regulation and guidance.

(G) Violation—If the responsible person or the holder of the approved application under subsection (j) of this section has not submitted a supplement within 15 days of the date of such order under subparagraph (E), and there is no appeal or dispute resolution proceeding pending, the responsible person or holder shall be considered to be in violation of this subsection. If at the conclusion of any dispute resolution procedures the Secretary determines that a supplement must be submitted and such a supplement is not submitted within 15 days of the date of that determination, the responsible person or holder shall be in violation of this subsection.

(H) Public health threat—Notwithstanding subparagraphs (A) through (F), if the Secretary concludes that such a labeling change is necessary to protect the public health, the Secretary may accelerate the timelines in such subparagraphs.

(I) Rule of construction—This paragraph shall not be construed to affect the responsibility of the responsible person or the holder of the approved application under subsection (j) of this section to maintain its label in accordance with existing requirements, including subpart B of part 201 and sections 314.70 and

601.12 of title 21, Code of Federal Regulations (or any successor regulations).

(5) Non-delegation—Determinations by the Secretary under this subsection for a drug shall be made by individuals at or above the level of individuals empowered to approve a drug (such as division directors within the Center for Drug Evaluation and Research).

(p) Risk evaluation and mitigation strategy

(1) In general—A person may not introduce or deliver for introduction into interstate commerce a new drug if—

(A)(i) the application for such drug is approved under subsection (b) or (j) of this section and is subject to section 353(b) of this title; or

(ii) the application for such drug is approved under section 262 of Title 42; and

(B) a risk evaluation and mitigation strategy is required under section 355-1 of this title with respect to the drug and the person fails to maintain compliance with the requirements of the approved strategy or with other requirements under section 355-1 of this title, including requirements regarding assessments of approved strategies.

(2) Certain postmarket studies—The failure to conduct a postmarket study under section 356 of this title, subpart H of part 314, or subpart E of part 601 of title 21, Code of Federal Regulations (or any successor regula-

tions), is deemed to be a violation of paragraph (1).

(q) Petitions and civil actions regarding approval of certain applications

(1) In general

(A) Determination—The Secretary shall not delay approval of a pending application submitted under subsection (b)(2) or (j) of this section because of any request to take any form of action relating to the application, either before or during consideration of the request, unless—

(i) the request is in writing and is a petition submitted to the Secretary pursuant to section 10.30 or 10.35 of title 21, Code of Federal Regulations (or any successor regulations); and

(ii) the Secretary determines, upon reviewing the petition, that a delay is necessary to protect the public health.

Consideration of the petition shall be separate and apart from review and approval of any application.

(B) Notification—If the Secretary determines under subparagraph (A) that a delay is necessary with respect to an application, the Secretary shall provide to the applicant, not later than 30 days after making such determination, the following information:

(i) Notification of the fact that a determination under subparagraph (A) has been made.

(ii) If applicable, any clarification or additional data that the applicant should submit to the docket on the petition to allow the Secretary to review the petition promptly.

(iii) A brief summary of the specific substantive issues raised in the petition which form the basis of the determination.

(C) Format—The information described in subparagraph (B) shall be conveyed via either, at the discretion of the Secretary—

(i) a document; or

(ii) a meeting with the applicant involved.

(D) Public disclosure—Any information conveyed by the Secretary under subparagraph (C) shall be considered part of the application and shall be subject to the disclosure requirements applicable to information in such application.

(E) Denial based on intent to delay—If the Secretary determines that a petition or a supplement to the petition was submitted with the primary purpose of delaying the approval of an application and the petition does not on its face raise valid scientific or regulatory issues, the Secretary may deny the petition at any point based

on such determination. The Secretary may issue guidance to describe the factors that will be used to determine under this subparagraph whether a petition is submitted with the primary purpose of delaying the approval of an application.

(F) Final agency action—The Secretary shall take final agency action on a petition not later than 180 days after the date on which the petition is submitted. The Secretary shall not extend such period for any reason, including—

(i) any determination made under subparagraph (A);

(ii) the submission of comments relating to the petition or supplemental information supplied by the petitioner; or

(iii) the consent of the petitioner.

(G) Extension of 30-month period—If the filing of an application resulted in first-applicant status under subsection (j)(5)(D)(i)(IV) of this section and approval of the application was delayed because of a petition, the 30-month period under such subsection is deemed to be extended by a period of time equal to the period beginning on the date on which the Secretary received the petition and ending on the date of final agency action on the petition (inclusive of such beginning and ending dates), without regard to whether the Secretary grants, in whole or in part,

or denies, in whole or in part, the petition.

(H) Certification—The Secretary shall not consider a petition for review unless the party submitting such petition does so in written form and the subject document is signed and contains the following certification: "I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: _____. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: _____. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.", with the date on which such information first became known to such party and the names of such persons or organizations inserted

in the first and second blank space, respectively.

(I) Verification—The Secretary shall not accept for review any supplemental information or comments on a petition unless the party submitting such information or comments does so in written form and the subject document is signed and contains the following verification: "I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about _____. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: _____. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.", with the date on which such information first became known to the party and the names of such persons or organizations inserted in the first and second blank space, respectively.

(2) Exhaustion of administrative remedies

(A) Final agency action within 180 days –The Secretary shall be considered to have taken final agency action on a petition if—

(i) during the 180-day period referred to in paragraph (1)(F), the Secretary makes a final decision within the meaning of section 10.45(d) of title 21, Code of Federal Regulations (or any successor regulation); or

(ii) such period expires without the Secretary having made such a final decision.

(B) Dismissal of certain civil actions—If a civil action is filed against the Secretary with respect to any issue raised in the petition before the Secretary has taken final agency action on the petition within the meaning of subparagraph (A), the court shall dismiss without prejudice the action for failure to exhaust administrative remedies.

(C) Administrative record—For purposes of judicial review related to the approval of an application for which a petition under paragraph (1) was submitted, the administrative record regarding any issue raised by the petition shall include—

(i) the petition filed under paragraph (1) and any supplements and comments thereto;

(ii) the Secretary's response to such petition, if issued; and

(iii) other information, as designated by the Secretary, related to the Secretary's determinations regarding the issues raised in such petition, as long

as the information was considered by the agency no later than the date of final agency action as defined under subparagraph (2)(A), and regardless of whether the Secretary responded to the petition at or before the approval of the application at issue in the petition.

(3) Annual report on delays in approvals per petitions—The Secretary shall annually submit to the Congress a report that specifies—

(A) the number of applications that were approved during the preceding 12-month period;

(B) the number of such applications whose effective dates were delayed by petitions referred to in paragraph (1) during such period;

(C) the number of days by which such applications were so delayed; and

(D) the number of such petitions that were submitted during such period.

(4) Exceptions—This subsection does not apply to—

(A) a petition that relates solely to the timing of the approval of an application pursuant to subsection (j)(5)(B)(iv) of this section; or

(B) a petition that is made by the sponsor of an application and that seeks only to have the Secretary take or refrain from

taking any form of action with respect to that application.

(5) Definitions

(A) Application—For purposes of this subsection, the term "application" means an application submitted under subsection (b)(2) or (j) of this section.

(B) Petition—For purposes of this subsection, other than paragraph (1)(A)(i), the term "petition" means a request described in paragraph (1)(A)(i).

(r) Postmarket drug safety information for patients and providers

(1) Establishment—Not later than 1 year after September 27, 2007, the Secretary shall improve the transparency of information about drugs and allow patients and health care providers better access to information about drugs by developing and maintaining an Internet Web site that—

(A) provides links to drug safety information listed in paragraph (2) for prescription drugs that are approved under this section or licensed under section 262 of Title 42; and

(B) improves communication of drug safety information to patients and providers.

(2) Internet Web site—The Secretary shall carry out paragraph (1) by—

(A) developing and maintaining an accessible, consolidated Internet Web site with easily searchable drug safety informa-

tion, including the information found on United States Government Internet Web sites, such as the United States National Library of Medicine's Daily Med and Medline Plus Web sites, in addition to other such Web sites maintained by the Secretary;

(B) ensuring that the information provided on the Internet Web site is comprehensive and includes, when available and appropriate—

(i) patient labeling and patient packaging inserts;

(ii) a link to a list of each drug, whether approved under this section or licensed under such section 262, for which a Medication Guide, as provided for under part 208 of title 21, Code of Federal Regulations (or any successor regulations), is required;

(iii) a link to the registry and results data bank provided for under subsections (i) and (j) of section 282 of Title 42;

(iv) the most recent safety information and alerts issued by the Food and Drug Administration for drugs approved by the Secretary under this section, such as product recalls, warning letters, and import alerts;

(v) publicly available information about implemented RiskMAPs and risk evaluation and mitigation strategies under subsection (o) of this section;

(vi) guidance documents and regulations related to drug safety; and

(vii) other material determined appropriate by the Secretary;

(C) providing access to summaries of the assessed and aggregated data collected from the active surveillance infrastructure under subsection (k)(3) of this section to provide information of known and serious side-effects for drugs approved under this section or licensed under such section 262 of Title 42;

(D) preparing, by 18 months after approval of a drug or after use of the drug by 10,000 individuals, whichever is later, a summary analysis of the adverse drug reaction reports received for the drug, including identification of any new risks not previously identified, potential new risks, or known risks reported in unusual number;

(E) enabling patients, providers, and drug sponsors to submit adverse event reports through the Internet Web site;

(F) providing educational materials for patients and providers about the appropriate means of disposing of expired, damaged, or unusable medications; and

(G) supporting initiatives that the Secretary determines to be useful to fulfill the purposes of the Internet Web site.

(3) Posting of drug labeling—The Secretary shall post on the Internet Web site established un-

der paragraph (1) the approved professional labeling and any required patient labeling of a drug approved under this section or licensed under such section 262 of Title 42 not later than 21 days after the date the drug is approved or licensed, including in a supplemental application with respect to a labeling change.

(4) Private sector resources—To ensure development of the Internet Web site by the date described in paragraph (1), the Secretary may, on a temporary or permanent basis, implement systems or products developed by private entities.

(5) Authority for contracts—The Secretary may enter into contracts with public and private entities to fulfill the requirements of this subsection.

(6) Review—The Advisory Committee on Risk Communication under section 360bbb-6 of this title shall, on a regular basis, perform a comprehensive review and evaluation of the types of risk communication information provided on the Internet Web site established under paragraph (1) and, through other means, shall identify, clarify, and define the purposes and types of information available to facilitate the efficient flow of information to patients and providers, and shall recommend ways for the Food and Drug Administration to work with outside entities to help facilitate the dispensing of risk communication information to patients and providers.

(s) Referral to advisory committee

Prior to the approval of a drug no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under this section or section 262 of Title 42, the Secretary shall—

(1) refer such drug to a Food and Drug Administration advisory committee for review at a meeting of such advisory committee; or

(2) if the Secretary does not refer such a drug to a Food and Drug Administration advisory committee prior to the approval of the drug, provide in the action letter on the application for the drug a summary of the reasons why the Secretary did not refer the drug to an advisory committee prior to approval.

(t) Database for authorized generic drugs

(1) In general

(A) Publication—The Commissioner shall—

(i) not later than 9 months after September 27, 2007, publish a complete list on the Internet Web site of the Food and Drug Administration of all authorized generic drugs (including drug trade name, brand company manufacturer, and the date the authorized generic drug entered the market); and

(ii) update the list quarterly to include each authorized generic drug included in an annual report submitted to the Secretary by the sponsor of a

listed drug during the preceding 3-month period.

(B) Notification—The Commissioner shall notify relevant Federal agencies, including the Centers for Medicare & Medicaid Services and the Federal Trade Commission, when the Commissioner first publishes the information described in subparagraph (A) that the information has been published and that the information will be updated quarterly.

(2) Inclusion—The Commissioner shall include in the list described in paragraph (1) each authorized generic drug included in an annual report submitted to the Secretary by the sponsor of a listed drug after January 1, 1999.

(3) Authorized generic drug—In this section, the term "authorized generic drug" means a listed drug (as that term is used in subsection (j) of this section) that--

(A) has been approved under subsection (c) of this section; and

(B) is marketed, sold, or distributed directly or indirectly to retail class of trade under a different labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trade mark than the listed drug.

(u) Certain drugs containing single enantiomers

(1) In general—For purposes of subsections (c)(3)(E)(ii) and (j)(5)(F)(ii) of this section, if an application is submitted under subsection (b) of this section for a non-racemic drug containing as an active ingredient (including any ester or salt of the active ingredient) a single enantiomer that is contained in a racemic drug approved in another application under subsection (b) of this section, the applicant may, in the application for such non-racemic drug, elect to have the single enantiomer not be considered the same active ingredient as that contained in the approved racemic drug, if—

(A)(i) the single enantiomer has not been previously approved except in the approved racemic drug; and

(ii) the application submitted under subsection (b) of this section for such non-racemic drug—

(I) includes full reports of new clinical investigations (other than bioavailability studies)—

(aa) necessary for the approval of the application under subsections (c) and (d) of this section; and

(bb) conducted or sponsored by the applicant; and

(II) does not rely on any investigations that are part of an applica-

tion submitted under subsection (b) of this section for approval of the approved racemic drug; and

(B) the application submitted under subsection (b) of this section for such non-racemic drug is not submitted for approval of a condition of use—

(i) in a therapeutic category in which the approved racemic drug has been approved; or

(ii) for which any other enantiomer of the racemic drug has been approved.

(2) Limitation

(A) No approval in certain therapeutic categories—Until the date that is 10 years after the date of approval of a non-racemic drug described in paragraph (1) and with respect to which the applicant has made the election provided for by such paragraph, the Secretary shall not approve such non-racemic drug for any condition of use in the therapeutic category in which the racemic drug has been approved.

(B) Labeling—If applicable, the labeling of a non-racemic drug described in paragraph (1) and with respect to which the applicant has made the election provided for by such paragraph shall include a statement that the non-racemic drug is not approved, and has not been shown to be safe and effective, for any condition of use of the racemic drug.

(3) Definition

(A) In general—For purposes of this subsection, the term "therapeutic category" means a therapeutic category identified in the list developed by the United States Pharmacopeia pursuant to section 1395w-104(b)(3)(C)(ii) of Title 42 and as in effect on September 27, 2007.

(B) Publication by Secretary—The Secretary shall publish the list described in subparagraph (A) and may amend such list by regulation.

(4) Availability—The election referred to in paragraph (1) may be made only in an application that is submitted to the Secretary after September 27, 2007, and before October 1, 2012.

(v) Antibiotic drugs submitted before November 21, 1997

(1) Antibiotic drugs approved before November 21, 1997

(A) In general—Notwithstanding any provision of the Food and Drug Administration Modernization Act of 1997 or any other provision of law, a sponsor of a drug that is the subject of an application described in subparagraph (B)(i) shall be eligible for, with respect to the drug, the 3-year exclusivity period referred to under clauses (iii) and (iv) of subsection (c)(3)(E) and under clauses (iii) and (iv) of subsection (j)(5)(F), subject to the requirements of such clauses, as applicable.

(B) Application; antibiotic drug described

(i) Application—An application described in this clause is an application for marketing submitted under this section after October 8, 2008 in which the drug that is the subject of the application contains an antibiotic drug described in clause (ii).

(ii) Antibiotic drug—An antibiotic drug described in this clause is an antibiotic drug that was the subject of an application approved by the Secretary under section 357 of this title (as in effect before November 21, 1997).

(2) Antibiotic drugs submitted before November 21, 1997, but not approved

(A) In general—Notwithstanding any provision of the Food and Drug Administration Modernization Act of 1997 or any other provision of law, a sponsor of a drug that is the subject of an application described in subparagraph (B)(i) may elect to be eligible for, with respect to the drug—

(i)(I) the 3-year exclusivity period referred to under clauses (iii) and (iv) of subsection (c)(3)(E) and under clauses (iii) and (iv) of subsection (j)(5)(F), subject to the requirements of such clauses, as applicable; and

(II) the 5-year exclusivity period referred to under clause (ii) of subsection (c)(3)(E) and under clause

(ii) of subsection (j)(5)(F), subject to the requirements of such clauses, as applicable; or

(ii) a patent term extension under section 156 of Title 35 subject to the requirements of such section.

(B) Application; antibiotic drug described

(i) Application—An application described in this clause is an application for marketing submitted under this section after October 8, 2008 in which the drug that is the subject of the application contains an antibiotic drug described in clause (ii).

(ii) Antibiotic drug—An antibiotic drug described in this clause is an antibiotic drug that was the subject of 1 or more applications received by the Secretary under section 357 of this title (as in effect before November 21, 1997), none of which was approved by the Secretary under such section.

(3) Limitations

(A) Exclusivities and extensions—Paragraphs (1)(A) and (2)(A) shall not be construed to entitle a drug that is the subject of an approved application described in subparagraphs (1)(B)(i) or (2)(B)(i), as applicable, to any market exclusivities or patent extensions other than those exclusivities or extensions described in paragraph (1)(A) or (2)(A).

(B) Conditions of use—Paragraphs (1)(A) and (2)(A)(i) shall not apply to any condition of use for which the drug referred to in subparagraph (1)(B)(i) or (2)(B)(i), as applicable, was approved before October 8, 2008.

(4) Application of certain provisions—Notwithstanding section 125, or any other provision, of the Food and Drug Administration Modernization Act of 1997, or any other provision of law, and subject to the limitations in paragraphs (1), (2), and (3), the provisions of the Drug Price Competition and Patent Term Restoration Act of 1984 shall apply to any drug subject to paragraph (1) or any drug with respect to which an election is made under paragraph (2)(A).

CODE OF FEDERAL REGULATIONS

TITLE 21—FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Part 314. Applications for FDA Approval to Market a New Drug—

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Subpart B. Applications

Sec. 314.53 Submission of patent information.

(a) Who must submit patent information. This section applies to any applicant who submits to FDA a new drug application or an amendment to it under section 505(b) of the act and § 314.50 or a supplement to an approved application under § 314.70, except as provided in paragraph (d)(2) of this section.

(b) Patents for which information must be submitted and patents for which information must not be submitted—

(1) General requirements. An applicant described in paragraph (a) of this section shall submit the required information on the declaration form set forth in paragraph (c) of this section for each patent that claims the drug or a method of using the drug that is the subject of the new drug application or amendment or supplement to it and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. For purposes of this part, such patents consist of drug substance (active ingredient) patents, drug prod-

uct (formulation and composition) patents, and method-of-use patents. For patents that claim the drug substance, the applicant shall submit information only on those patents that claim the drug substance that is the subject of the pending or approved application or that claim a drug substance that is the same as the active ingredient that is the subject of the approved or pending application. For patents that claim a polymorph that is the same as the active ingredient described in the approved or pending application, the applicant shall certify in the declaration forms that the applicant has test data, as set forth in paragraph (b)(2) of this section, demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the new drug application. For patents that claim a drug product, the applicant shall submit information only on those patents that claim a drug product, as is defined in § 314.3, that is described in the pending or approved application. For patents that claim a method of use, the applicant shall submit information only on those patents that claim indications or other conditions of use that are described in the pending or approved application. The applicant shall separately identify each pending or approved method of use and related patent claim. For approved applications, the applicant submitting the method-of-use patent shall identify with specificity the section of the approved labeling that corresponds to the method of use claimed by the patent submitted. Process patents, patents claiming packaging, patents claiming metabolites, and patents claiming intermediates are not covered by this section, and information on these patents must not be submitted to FDA.

(2) Test Data for Submission of Patent Information for Patents That Claim a Polymorph. The test data, referenced in paragraph (b)(1) of this section, must include the following:

(i) A full description of the polymorphic form of the drug substance, including its physical and chemical characteristics and stability; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and such specifications and analytical methods as are necessary to assure the identity, strength, quality, and purity of the polymorphic form of the drug substance;

(ii) The executed batch record for a drug product containing the polymorphic form of the drug substance and documentation that the batch was manufactured under current good manufacturing practice requirements;

(iii) Demonstration of bioequivalence between the executed batch of the drug product that contains the polymorphic form of the drug substance and the drug product as described in the NDA;

(iv) A list of all components used in the manufacture of the drug product containing the polymorphic form and a statement of the composition of the drug product; a statement of the specifications and analytical methods for each component; a description of the manufacturing and packaging procedures and in-process controls for the drug product; such specifications and analytical methods as are necessary to assure the identity, strength, quality, purity, and

bioavailability of the drug product, including release and stability data complying with the approved product specifications to demonstrate pharmaceutical equivalence and comparable product stability; and

(v) Comparative in vitro dissolution testing on 12 dosage units each of the executed test batch and the new drug application product.

(c) Reporting requirements—

(1) General requirements. An applicant described in paragraph (a) of this section shall submit the required patent information described in paragraph (c)(2) of this section for each patent that meets the requirements described in paragraph (b) of this section. We will not accept the patent information unless it is complete and submitted on the appropriate forms, FDA Forms 3542 or 3542a. These forms may be obtained on the Internet at http://www.fda.gov by searching for "forms".

(2) Drug substance (active ingredient), drug product (formulation or composition), and method-of-use patents—

(i) Original Declaration. For each patent that claims a drug substance (active ingredient), drug product (formulation and composition), or method of use, the applicant shall submit FDA Form 3542a. The following information and verification is required:

(A) New drug application number;

(B) Name of new drug application sponsor;

(C) Trade name (or proposed trade name) of new drug;

(D) Active ingredient(s) of new drug;

(E) Strength(s) of new drug;

(F) Dosage form of new drug;

(G) United States patent number, issue date, and expiration date of patent submitted;

(H) The patent owner's name, full address, phone number and, if available, fax number and e-mail address;

(I) The name, full address, phone number and, if available, fax number and e-mail address of an agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under sections 505(b)(3) and 505(j)(2)(B) of the act and §§ 314.52 and 314.95 (if patent owner or new drug application applicant or holder does not reside or have a place of business within the United States);

(J) Information on whether the patent has been submitted previously for the new drug application;

(K) Information on whether the expiration date is a new expiration date if the patent had been submitted previously for listing;

(L) Information on whether the patent is a product-by-process patent in which the product claimed is novel;

(M) Information on the drug substance (active ingredient) patent including the following:

(1) Whether the patent claims the drug substance that is the active ingredient in the drug product described in the new drug application or supplement;

(2) Whether the patent claims a polymorph that is the same active ingredient that is described in the pending application or supplement;

(3) Whether the applicant has test data, described in paragraph (b)(2) of this section, demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the new drug application or supplement, and a description of the polymorphic form(s) claimed by the patent for which such test data exist;

(4) Whether the patent claims only a metabolite of the active ingredient; and

(5) Whether the patent claims only an intermediate;

(N) Information on the drug product (composition/formulation) patent including the following:

(1) Whether the patent claims the drug product for which approval is being sought, as defined in § 314.3; and

(2) Whether the patent claims only an intermediate;

(O) Information on each method-of-use patent including the following:

(1) Whether the patent claims one or more methods of using the drug product for which use approval is being sought and a description of each pending method of use or related indication and related patent claim of the patent being submitted; and

(2) Identification of the specific section of the proposed labeling for the drug product that corresponds to the method of use claimed by the patent submitted;

(P) Whether there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product;

(Q) A signed verification which states: "The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct."; and

(R) Information on whether the applicant, patent owner or attorney, agent, representative or other authorized official signed the form; the name of the person; and the full address, phone number and, if available, the fax number and e-mail address.

(ii) Submission of patent information upon and after approval. Within 30 days after the date of approval of its application or supplement, the applicant shall submit FDA Form 3542 for each patent that claims the drug substance (active ingredient), drug product (formulation and composition), or approved method of use. FDA will rely only on the information submitted on this form and will not list or publish patent information if the patent declaration is incomplete or indicates the patent is not eligible for listing. Patent information must also be submitted for patents issued after the date of approval of the new drug application as required in paragraph (c)(2)(ii) of this section. As described in paragraph (d)(4) of this section, patent information must be submitted to FDA within 30 days of the date of issuance of the patent. If the applicant submits the required patent information within the 30 days, but we notify an applicant that a declaration form is incomplete or shows that the patent is not eligible for listing, the applicant must submit an acceptable declaration form within 15 days of FDA notification to be considered timely filed. The following information and verification statement is required:

(A) New drug application number;

(B) Name of new drug application sponsor;

(C) Trade name of new drug;

(D) Active ingredient(s) of new drug;

(E) Strength(s) of new drug;

(F) Dosage form of new drug;

(G) Approval date of new drug application or supplement;

(H) United States patent number, issue date, and expiration date of patent submitted;

(I) The patent owner's name, full address, phone number and, if available, fax number and e-mail address;

(J) The name, full address, phone number and, if available, fax number and e-mail address of an agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under sections 505(b)(3) and 505(j)(2)(B) of the act and §§ 314.52 and 314.95 (if patent owner or new drug application applicant or holder does not reside or have a place of business within the United States);

(K) Information on whether the patent has been submitted previously for the new drug application;

(L) Information on whether the expiration date is a new expiration date if the patent had been submitted previously for listing;

(M) Information on whether the patent is a product-by-process patent in which the product claimed is novel;

(N) Information on the drug substance (active ingredient) patent including the following:

(1) Whether the patent claims the drug substance that is the active ingredient in the drug product described in the approved application;

(2) Whether the patent claims a polymorph that is the same as the active ingredient that is described in the approved application;

(3) Whether the applicant has test data, described at paragraph (b)(2) of this section, demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the approved application and a description of the polymorphic form(s) claimed by the patent for which such test data exist;

(4) Whether the patent claims only a metabolite of the active ingredient; and

(5) Whether the patent claims only an intermediate;

(O) Information on the drug product (composition/formulation) patent including the following:

(1) Whether the patent claims the approved drug product as defined in § 314.3; and

(2) Whether the patent claims only an intermediate;

(P) Information on each method-of-use patent including the following:

(1) Whether the patent claims one or more approved methods of using the approved drug product and a description of each approved method of use or indication and related patent claim of the patent being submitted;

(2) Identification of the specific section of the approved labeling for the drug product that corresponds to the method of use claimed by the patent submitted; and

(3) The description of the patented method of use as required for publication;

(Q) Whether there are no relevant patents that claim the approved drug substance (active ingredient), the approved drug product (formulation or composition) or approved method(s) of use and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product;

(R) A signed verification which states: "The undersigned declares that this is an accurate and complete submission of patent in-

formation for the NDA, amendment or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct."; and

(S) Information on whether the applicant, patent owner or attorney, agent, representative or other authorized official signed the form; the name of the person; and the full address, phone number and, if available, the fax number and e-mail address.

(3) No relevant patents. If the applicant believes that there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition), or the method(s) of use for which the applicant has received approval, and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product, the applicant will verify this information in the appropriate forms, FDA Forms 3542 or 3542a.

(4) Authorized signature. The declarations required by this section shall be signed by the applicant or patent owner, or the applicant's or patent owner's at-

torney, agent (representative), or other authorized official.

(d) When and where to submit patent information--

(1) Original application. An applicant shall submit with its original application submitted under this part, including an application described in section 505(b)(2) of the act, the information described in paragraph (c) of this section on each drug (ingredient), drug product (formulation and composition), and method of use patent issued before the application is filed with FDA and for which patent information is required to be submitted under this section. If a patent is issued after the application is filed with FDA but before the application is approved, the applicant shall, within 30 days of the date of issuance of the patent, submit the required patent information in an amendment to the application under § 314.60.

(2) Supplements.

(i) An applicant shall submit patent information required under paragraph (c) of this section for a patent that claims the drug, drug product, or method of use for which approval is sought in any of the following supplements:

(A) To change the formulation;

(B) To add a new indication or other condition of use, including a change in route of administration;

(C) To change the strength;

(D) To make any other patented change regarding the drug, drug product, or any method of use.

(ii) If the applicant submits a supplement for one of the changes listed under paragraph (d)(2)(i) of this section and existing patents for which information has already been submitted to FDA claim the changed product, the applicant shall submit a certification with the supplement identifying the patents that claim the changed product.

(iii) If the applicant submits a supplement for one of the changes listed under paragraph (d)(2)(i) of this section and no patents, including previously submitted patents, claim the changed product, it shall so certify.

(iv) The applicant shall comply with the requirements for amendment of formulation or composition and method of use patent information under paragraphs (c)(2)(ii) and (d)(3) of this section.

(3) Patent information deadline. If a patent is issued for a drug, drug product, or method of use after an application is approved, the applicant shall submit to FDA the required patent information within 30 days of the date of issuance of the patent.

(4) Copies. The applicant shall submit two copies of each submission of patent information, an archival copy and a copy for the chemistry, manufacturing, and controls section of the review copy, to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266. The applicant shall submit the patent information by letter separate from, but at the same time as, submission of the supplement.

(5) Submission date. Patent information shall be considered to be submitted to FDA as of the date the information is received by the Central Document Room.

(6) Identification. Each submission of patent information, except information submitted with an original application, and its mailing cover shall bear prominent identification as to its contents, i.e., "Patent Information," or, if submitted after approval of an application, "Time Sensitive Patent Information."

(e) Public disclosure of patent information. FDA will publish in the list the patent number and expiration date of each patent that is required to be, and is, submitted to FDA by an applicant, and for each use patent, the approved indications or other conditions of use covered by a patent. FDA will publish such patent information upon approval of the application, or, if the patent information is submitted by the applicant after approval of an application as provided under paragraph (d)(2) of this section, as soon as possible after the submission to the agency of the patent information. Patent information submitted by the last working day of a month will be published in that month's supplement to the list. Patent information received by the Agency between monthly publication of supplements to the list will be placed on public display in FDA's Division of Freedom of Information. A request for copies of the file shall be sent in writing to the Division of Freedom of Information (ELEM-1029), Food and Drug Administration, 12420 Parklawn Dr., Element Bldg., Rockville, MD 20857.

(f) Correction of patent information errors. If any person disputes the accuracy or relevance of patent in-

formation submitted to the agency under this section and published by FDA in the list, or believes that an applicant has failed to submit required patent information, that person must first notify the agency in writing stating the grounds for disagreement. Such notification should be directed to the Office of Generic Drugs, OGD Document Room, Attention: Orange Book Staff, at the address identified on FDA's Web site 7500 Standish Pl., Rockville, MD 20855. The agency will then request of the applicable new drug application holder that the correctness of the patent information or omission of patent information be confirmed. Unless the application holder withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in the list. If the new drug application holder does not change the patent information submitted to FDA, a 505(b)(2) application or an abbreviated new drug application under section 505(j) of the act submitted for a drug that is claimed by a patent for which information has been submitted must, despite any disagreement as to the correctness of the patent information, contain an appropriate certification for each listed patent.

[59 FR 50363, Oct. 3, 1994; 68 FR 36703, June 18, 2003; 69 FR 13473, March 23, 2004; 74 FR 9766, March 6, 2009; 74 FR 36605, July 24, 2009; 76 FR31470, June 1, 2011]

RESPONDENT'S BRIEF

Supreme Court, U.S.
FILED
OCT 17 2011
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No. 10-844

IN THE

Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD. AND SUN PHARMACEUTICAL INDUSTRIES, LTD.,

Petitioners,

v.

NOVO NORDISK A/S AND NOVO NORDISK INC.,

Respondents.

On Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

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QUESTION PRESENTED

Under the Hatch-Waxman Act's counterclaim provision, if (1) the generic challenger maintains a "Paragraph IV" certification as to the patent claim-in-suit and (2) the generic challenger both (a) proves that the patent "does not claim ... an approved method of using the drug" and (b) challenges "the patent information submitted ... under" particular statutory provisions, then (3) the generic challenger may seek a judicial order requiring the patentee to "correct or delete" the specified information. 21 U.S.C. § 355(j)(5)(C)(ii).

In this case, (1) the generic challenger withdrew its Paragraph IV certification before initiating the counterclaim; (2) the generic challenger (a) concedes that the patent *does* claim an approved method of using the drug and (b) challenges the "use code narrative," which is not statutory "patent information"; and (3) the generic challenger seeks "correct[ion]" of a single entry on a notification form that complies with all applicable statutory and regulatory requirements and guidance.

The question presented is whether the Federal Circuit correctly concluded that the counterclaim is not available in these circumstances.

RULE 29.6 STATEMENT

The corporate disclosure statement included in the brief in opposition remains accurate.

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BRIEF FOR RESPONDENTS

Respondents Novo Nordisk A/S and Novo Nordisk Inc. respectfully submit that the judgment of the court of appeals should be affirmed or, alternatively, vacated and remanded with instructions to dismiss for lack of jurisdiction.

JURISDICTION

Petitioners invoke the jurisdiction of this Court under 28 U.S.C. § 1254(1). As explained in Argument Part I, *infra*, the federal courts lack subject-matter jurisdiction over this dispute.

STATUTORY PROVISIONS INVOLVED

The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, commonly known as the Hatch-Waxman Act, amended various provisions of the Federal Food, Drug, and Cosmetic Act (FDCA), including 21 U.S.C. § 355 (Pet. App. 104a-195a), and the Patent Act, including 35 U.S.C. § 271(e)(2)(A) (Opp. App. 108a-109a). The counterclaim provision at issue here (Pet. App. 145a-146a), added as part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066, states:

> **(ii) Counterclaim to infringement action**
>
> **(I) In general**
>
> If an owner of the patent or the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the [generic] applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the

> patent information submitted by the holder under subsection (b) or (c) of this section on the ground that the patent does not claim either—
>
> (aa) the drug for which the application was approved; or
>
> (bb) an approved method of using the drug.
>
> **(II) No independent cause of action**
>
> Subclause (I) does not authorize the assertion of a claim described in subclause (I) in any civil action or proceeding other than a counterclaim described in subclause (I).

21 U.S.C. § 355(j)(5)(C)(ii).

STATEMENT

The district court ordered respondents Novo Nordisk A/S and Novo Nordisk Inc. (collectively Novo) to alter the "use code narrative" published by the Food and Drug Administration in connection with Novo's patented method of diabetes drug therapy. Pet. App. 65a-66a. The Federal Circuit reversed, concluding that petitioners Caraco Pharmaceutical Laboratories, Ltd. and Sun Pharmaceutical Industries, Ltd. (collectively Caraco) do "not have a statutory basis to assert a counterclaim requesting such injunctive relief." *Id.* at 2a-3a.

The decision below turned on two narrow issues of statutory construction. *First*, Caraco could not establish the counterclaim's predicate that the "patent does not claim ... an approved method of using the drug" (21 U.S.C. § 355(j)(5)(C)(ii)) because Novo's patent *does* claim an approved method of using the drug at issue. Pet. App. 11a-14a. *Second*, the counterclaim provision does not authorize court-ordered

changes to Novo's use code narrative because the only "patent information submitted ... under subsection (b) or (c)" of 21 U.S.C. § 355—and thus the only information that can be "correct[ed] or delete[d]" pursuant to the counterclaim—is the patent number and expiration date. Pet. App. 14a-17a.

1. The Hatch-Waxman Act, originally enacted in 1984, governs many aspects of the intense competition among makers of branded and generic drugs. *See generally Janssen Pharmaceutica, N.V.* v. *Apotex, Inc.*, 540 F.3d 1353, 1355-57 (Fed. Cir. 2008). In particular, Section 505 of the FDCA, as amended by Hatch-Waxman, regulates the process by which drug makers can secure FDA approval of new drugs, as well as the avenues of judicial relief available to patent holders and their generic competitors. *See* 21 U.S.C. § 355.

a. Section 505(a) prohibits the sale of a new drug "unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug." 21 U.S.C. § 355(a). Subsection (b) requires a pioneer company seeking to manufacture a new drug to file a New Drug Application (NDA), together with a variety of information on safety and effectiveness. *Id.* § 355(b)(1)(A)-(G). And subsection (c), in turn, addresses amendments to and approval of NDAs, and authorizes certain lawsuits by the NDA holder to enforce its rights. *Id.* § 355(c)(1)-(3).

Section 505(b) requires NDA filers to provide FDA with specified "patent information": "The applicant shall file with the application the *patent number* and the *expiration date* of any patent which claims the drug ... or which claims a method of using such drug." 21 U.S.C. § 355(b)(1)(G) (emphases added).

Section 505(c) states that "[i]f the patent information described in subsection (b) of this section could not be filed with the submission of an application," the holder of an approved application "shall file with the Secretary the *patent number* and the *expiration date* of any patent which claims the drug ... or which claims a method of using such drug." *Id.* § 355(c)(2) (emphases added).

FDA publishes a list of patents claiming approved drug products or methods, along with the statutory "patent information" and certain additional information required by regulation, in its "Approved Drug Products with Therapeutic Equivalence Evaluations"—commonly known as the "Orange Book." *See Janssen*, 540 F.3d at 1355; *see also* J.A. 500-95 (excerpts).

b. Section 505(j) allows generic competitors to market copies of approved drugs by filing an Abbreviated New Drug Application (ANDA). 21 U.S.C. § 355(j). The ANDA process "substantially shorten[s] the time and effort needed to obtain marketing approval" of a generic copy by allowing the applicant to rely on the research of the pioneer pharmaceutical company, thus "avoid[ing] the costly and time-consuming [safety and efficacy] studies required for a pioneer drug." *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661, 676 (1990).

Although the ANDA mechanism makes it easier for generic companies to go to market, it does not eliminate patent protections for pioneer companies. *See Teva Pharm. Indus. Ltd.* v. *Crawford*, 410 F.3d 51, 54 (D.C. Cir. 2005). Rather, generic companies seeking approval to copy patented drugs must certify that (I) no patent covering the listed drug has been listed in the Orange Book; (II) the patent has ex-

pired; (III) the patent will expire on a particular date and approval of the ANDA should be deferred until expiration; or (IV) the patent is invalid or will not be infringed by the manufacture, use, or sale of the generic drug. 21 U.S.C. § 355(j)(2)(A)(vii). The last of these options is commonly known as a Paragraph IV certification.

The filing of a Paragraph IV certification by an ANDA applicant is an act of patent infringement. 35 U.S.C. § 271(e)(2)(A); *see also Eli Lilly*, 496 U.S at 678. If the pioneer company initiates a timely suit, FDA may not approve the ANDA for 30 months. 21 U.S.C. § 355(j)(5)(B)(iii). As an incentive for generic companies to risk an infringement suit, the first company to submit a Paragraph IV certification for a particular drug receives a 180-day period of marketing exclusivity. *Id.* § 355(j)(5)(B)(iv).

If an ANDA applicant wants to market a listed drug only for uses that are not covered by any method-of-use patent, it can ask FDA to "carve out" of the proposed product label—which generally must be identical to the branded label (21 U.S.C. § 355(j)(2)(A)(v))—any patented uses by filing what is known as a section viii statement. *Id.* § 355(j)(2)(A)(viii). The generic thereby represents that the "patent poses no bar to approval of an ANDA because the applicant seeks to market the drug for a use other than the one encompassed by the patent." *Purepac Pharm. Co.* v. *Thompson*, 354 F.3d 877, 880 (D.C. Cir. 2004). "ANDA applicants [must] use *either* a paragraph IV certification *or* a section viii statement—they may not use both." *Ibid.*

2. The Hatch-Waxman Act carefully balances the competing interests of branded and generic drug companies. *See, e.g.*, *Abbott Labs.* v. *Young*, 920 F.2d

984, 985 (D.C. Cir. 1990). In 2003, Congress enacted the only significant adjustments to that balance since the statute's initial enactment, including the counterclaim at issue here.

The impetus for the counterclaim was a 2001 decision that there was no statutory authorization for a generic competitor to seek delisting of a patent from the Orange Book on the ground that it "did not claim ... an approved method of using" the drug. *Mylan Pharms., Inc.* v. *Thompson*, 268 F.3d 1323, 1331 (Fed. Cir. 2001). The congressional response to *Mylan* proceeded in several steps.

a. Senators Schumer and McCain introduced S. 812, the "Greater Access to Affordable Pharmaceuticals Act of 2002," which (as amended on July 11, 2002) sought to add a new provision governing the "Filing of Patent Information with the Food and Drug Administration." S. 812, 107th Cong. § 103 (2002). S. 812 would have required NDA holders to file an expanded list of "patent information" with FDA, including:

> (i) the patent number;
>
> (ii) the expiration date of the patent;
>
> (iii) with respect to each claim of the patent—
>
> > (I) whether the patent claims the drug or claims a method of using the drug; and
> >
> > (II) whether the claim covers—
> >
> > > (aa) a drug substance;
> > >
> > > (bb) a drug formulation;
> > >
> > > (cc) a drug composition; or
> > >
> > > (dd) a method of use;
>
> [and]

> (iv) if the patent claims a method of use, the approved use covered by the claim ....

Id. § 103(a)(2)(C). S. 812 also would have authorized ANDA applicants to bring a freestanding civil action for correction or deletion of this expanded list of statutorily required "patent information":

> A person that has filed an [ANDA] for a drug may bring a civil action against the holder of the approved application for the drug seeking an order requiring that the holder of the application amend the application—
>
> (I) to correct patent information filed under subparagraph (A); or
>
> (II) to delete the patent information in its entirety for the reason that—
>
> (aa) the patent does not claim the drug for which the application was approved; or
>
> (bb) the patent does not claim an approved method of using the drug.

Id. § 103(a)(2)(E).

The redefinition of "patent information" and accompanying civil action in S. 812 met a firestorm of opposition from Republican legislators. Senator Hatch, for example, criticized the proposed civil action as an "unwelcome foothold for trial lawyers to reach into the FDC Act" that would "create a parallel course of litigation to the well-established Paragraph IV patent contests." 148 Cong. Rec. S6991 (July 18, 2002). He also noted "concern[s] about the policy and potential effects" of "significantly expand[ing] the type of patent information that must be filed, including requiring very precise claim by claim certifications of what each particular patent covers." *Id.* at S6990; *see also, e.g.*, 148 Cong. Rec. S7633 (July 31,

2002) (Sen. Gregg); *id.* at S7644 (Sen. Grassley); 148 Cong. Rec. S7345 (July 25, 2002) (Sen. Hatch); 148 Cong. Rec. S6995 (July 18, 2002) (Sen. Frist).

President Bush likewise opposed S. 812, warning that the proposed civil action "would unnecessarily encourage litigation around the initial approval of new drugs and would complicate the process of filing and protecting patents on new drugs." *Statement of Administration Policy: S. 812—Greater Access to Affordable Pharmaceuticals Act* (July 18, 2002). FDA communicated the Administration's concerns to Congress and argued that the proposed civil action created an undesirable alternative by allowing ANDA holders "to file suit in lieu of certifying under par. IV." 148 Cong. Rec. S6823 (July 16, 2002) (Sen. Gregg) (quoting FDA memo).

On July 31, 2002, S. 812 passed the Senate on a 66-33 vote. 148 Cong. Rec. S7634 (July 31, 2002). Senator McCain, the bill's Republican co-sponsor, noted that "[t]he cause of action for generic manufacturers to 'delist' patents ... was added to S. 812 late in the process, and it is controversial." *Id.* at S7644-7645. Although he suggested that the provision might warrant further consideration in conference (*see ibid.*), the House of Representatives—in which the Republicans held a majority—declined to take action on S. 812 or three virtually identical bills. *See* H.R. 5311, 107th Cong. § 3(a)(2)(E) (2002); H.R. 5272, 107th Cong. § 2(a)(2)(E) (2002); H.R. 5350, 107th Cong. § 10 (2002).[1]

---

[1] Proponents of the civil action also tried—but failed—to move similar bills through Congress the following year. *See*

b. On July 30, 2002, one day before the Senate passed S. 812, the Federal Trade Commission issued a study examining drug competition under the Hatch-Waxman Act. *See* Fed. Trade Comm'n, *Generic Drug Entry Prior to Patent Expiration* (July 2002), *available at* http://www.ftc.gov/opa/2002/07/genericdrugstudy.shtm. The FTC's recommendations diverged from S. 812 in two critical respects. *First*, rather than changing the *statutory* "patent information" that NDA holders must file, the FTC recommended that FDA "clarify its listing requirements" by regulation or guidance. *Id.* at v; *see also id.* at A-39. *Second*, instead of a stand-alone private right of action, the FTC recommended that Congress allow "a generic applicant to raise listability issues as a counterclaim in the context of patent infringement litigation already initiated by the brand-name company in response to a [generic's] paragraph IV notice." *Id.* at v.

FDA responded on October 24, 2002 by issuing a proposed rule to require NDA applicants and holders to provide substantial additional information about patented drugs and methods not mandated by Section 505(b) or (c). *See* 67 Fed. Reg. 65,448 (Oct. 24, 2002). As relevant here, the proposed rule made clear that method-of-use patents could be submitted for listing in the Orange Book and, "[f]or each method of use claim identified," required the NDA applicant or holder to answer:

[Footnote continued from previous page]

S. 7, 108th Cong. § 201(a)(2)(E) (2003); S. 54, 108th Cong. § 3(a)(2)(E) (2003); H.R. 2640, 108th Cong. § 10(a)(2)(E) (2003).

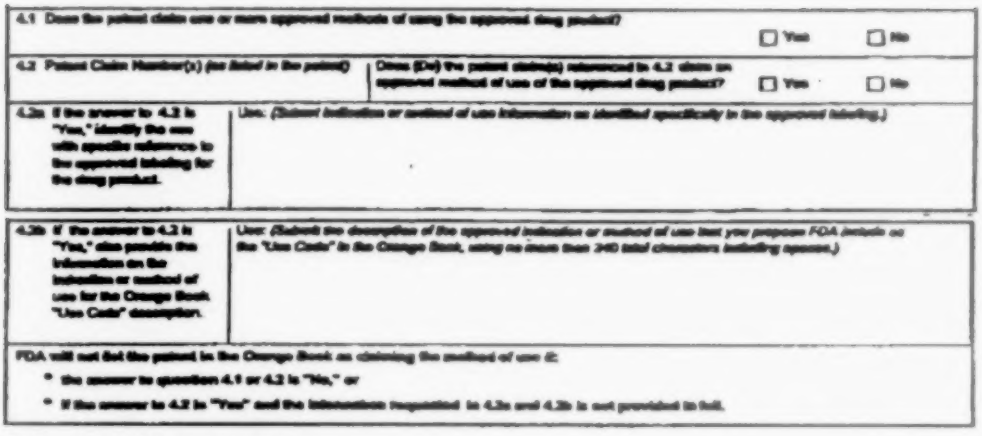
> Is the claim one that claims ... an approved method of use of the approved drug product?
>
> ——— Yes ——— No
>
> If ... "yes," please identify the use with reference to the approved labeling for the drug product and identify the relevant patent claim number(s).

Id. at 65,454. If the answer is "no," the proposed rule continued, "[t]he patent may not be listed in the Orange Book as a patent that claims a method of use." *Ibid.*

FDA issued its final rule on June 18, 2003. *See* 68 Fed. Reg. 36,676, 36,677 (June 18, 2003) (codified at 21 C.F.R. pt. 314). It requires the NDA holder to inform FDA "[w]hether the patent claims one or more approved methods of using the approved drug product." 21 C.F.R. § 314.53(c)(2)(ii)(P)(1). If so, then the NDA holder must also provide additional information, including a proposed "use code narrative"—a "description of each approved method of use or indication [*i.e.*, the disease or condition to be treated]." *Ibid.*

FDA implemented this rule in Form 3542. *See* Pet. App. 211a-214a; *see also* 68 Fed. Reg. at 36,711-12 (draft form). Using the "yes" or "no" format, Form 3542 requires NDA holders to declare, under penalty of perjury, whether or not the patent "claim[s] an approved method of use of the approved drug product." Pet. App. 212a. If the answer is "no," then the patent cannot be listed in the Orange Book. *See id.* at 213a. If the answer is "yes," then Form 3542 requires the submission of a "description of the approved indication or method of use" for a drug. *Ibid.*

Here is an excerpt from the form itself:



Id. at 212a-213a.

The use code narrative cannot exceed 240 characters because of "limitations [in FDA's] database system." 68 Fed. Reg. at 36,683. As FDA explained:

> Traditionally, we [FDA] have created the use code description for the Orange Book from the information submitted by the NDA applicant or holder. ... [W]e have determined that it is more efficient and accurate to ask the NDA holder to give us the exact use code description to be published in the Orange Book. *Use codes are intended to alert ANDA and 505(b)(2) applicants to the existence of a patent that claims an approved use. They are not meant to substitute for the applicant's review of the patent and the approved labeling. We understand that in some cases 240 characters may not fully describe the use as claimed in the patent.*

Ibid. (emphasis added).

c. After S. 812 failed, compromise legislation was drafted to address Republican objections and introduced by Senator Gregg as S. 1225 in June 2003. *See* 149 Cong. Rec. S8188 (June 19, 2003). Reflecting a

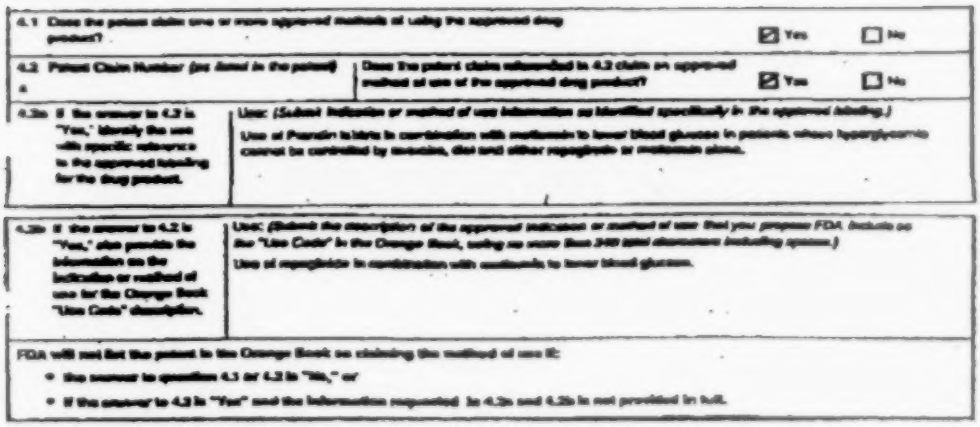
"carefully crafted bipartisan compromise" (*id.* at S8190), S. 1225 was significantly narrower than S. 812 and the other stalled bills. As Senator Schumer—a strong proponent of S. 812—acknowledged, the "modifications" in S. 1225 were necessary to "address the concerns that kept the bill's critics from supporting [S. 812] last year." *Examining the Senate and House Versions of the "Greater Access to Affordable Pharmaceuticals Act": Hearing Before the S. Comm. on the Judiciary*, 108th Cong. 1 (2003).

Rather than create a broad, independent cause of action to correct or delete an expanded list of statutorily required "patent information," S. 1225 allowed only a counterclaim, in a Paragraph IV suit for infringement, limited to correcting or deleting the patent number and expiration date. S. 1225, 108th Cong. § 2(a)(2)(C)(iii)(II)(aa) (2003). As the Conference Report explained, the counterclaim permits a generic "in a paragraph IV patent suit" to seek "removal of the patent" from the Orange Book. H.R. Rep. No. 108-391, at 836 (2003).

As enacted, the counterclaim echoes the language of *Mylan* in requiring the generic applicant to prove that the patent "does not claim ... the drug ... or ... an approved method of using the drug." 21 U.S.C. § 355(j)(5)(C)(ii)(I). If the generic applicant can carry this burden—that is, if it can prove that the patent was not properly listed in the Orange Book—it may "see[k] an order requiring the [patentee] to correct or delete the patent information submitted ... under subsection (b) or (c) of this section." *Ibid.*

3. Novo sells the diabetes drug repaglinide under the brand name PRANDIN®. Repaglinide is ap-

proved for treating diabetes when used alone (monotherapy) or in combination with other specified drugs, including metformin. J.A. 46. In 2004, Novo was issued U.S. Patent No. 6,677,358, Claim 4 of which claims a method for using repaglinide in combination with metformin to treat type 2 diabetes. *Id.* at 65-96. Only claim 4 is at issue in this litigation (*id.* at 367 ¶ 99); it, along with the rest of the '358 patent, will expire in 2018. *Id.* at 49. Novo submitted to FDA the statutory "patent information" along with a proposed use code narrative (*id.* at 98-99), which was published in the Orange Book as "U-546—Use of repaglinide in combination with metformin to lower blood glucose." *Id.* at 54-55. Novo's original Form 3542 stated in relevant part:



Id. at 98-99.

In 2005, Caraco filed an ANDA for generic repaglinide that included (at that time) a Paragraph IV certification that claim 4 of the '358 patent was invalid or would not be infringed by the sale of generic repaglinide. J.A. 116. Novo sued for infringement, and Caraco eventually stipulated that its ANDA for repaglinide would infringe the '358 patent if it "include[d] a label that discusses the combination of

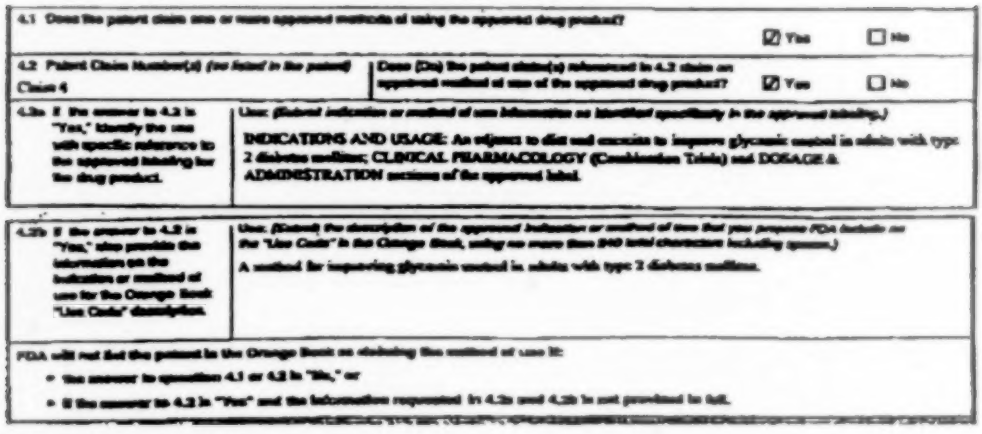
metformin and repaglinide." *Id.* at 177; *see also* Pet. 19 n.10.

In April 2008, Caraco amended its ANDA and, with respect to Claim 4, replaced its Paragraph IV certification with a section viii statement declaring that "Caraco ... does not seek approval for the use of Repaglinide in combination with Metformin to lower blood glucose." J.A. 175. Caraco sought to "carve out" all information relating to the repaglinide-metformin combination therapy from its otherwise infringing label. *Id.* at 250-55. In December 2008, FDA indicated that it would permit this carve-out. *Id.* at 257. Novo moved for reconsideration on the ground, *inter alia*, that the carved-out label would render generic repaglinide less safe and effective. *Id.* at 303-08; *see also id.* at 315-20.

During the same time period, Novo revised the PRANDIN® label pursuant to an FDA directive "requesting changes to the professional labeling of all oral anti-diabetic drugs." J.A. 163. FDA *required* Novo to "[r]eplace all the separate indications (e.g., monotherapy, combination therapy, and initial or second-line therapy) with the following sentence: 'Prandin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.'" *Id.* at 164.

In May 2009, after providing notice to FDA and in consultation with its regulatory counsel (J.A. 404, 407-09), Novo submitted an amended FDA Form 3542 "to amend the use code relating to [the '358 patent] to correspond with the change in labeling required by FDA in [its directive]." *Id.* at 483; *see also*

id. at 408. The amended Form 3542 states:



Id. at 485-86.

Caraco challenged the amended use code, invoking FDA's administrative review process under 21 C.F.R. § 314.53(f). *See* J.A. 331-39. FDA instituted the review procedures mandated by its regulation. *Id.* at 340-41, 374-75. Following that review, FDA accepted the revised use code and published it in the Orange Book: "U-968—A method for improving glycemic control in adults with type 2 diabetes mellitus." *Id.* at 592. Caraco did not seek judicial review of this FDA decision under the Administrative Procedure Act.

FDA then determined that Novo's request for reconsideration was "moot" in light of the new use code, as the "factual predicate" on which FDA's permissive decision had rested no longer applied. J.A. 369-73. FDA declined to allow Caraco to carve repaglinide-metformin combination therapy out of its label (*id.* at 377, 723), "because that would leave [Caraco's] labeling without any approved indication, rendering its drug not safe and effective." U.S. Br. 12. Instead, FDA directed Caraco to "submit an updated patent certification addressing the ['358] patent and its associated use code," and to amend its

ANDA to "[a]dd back" information about the combination therapy into the labeling. J.A. 377-78; *see also* 21 C.F.R. § 314.53(f) (ANDA must "contain an appropriate certification for each listed patent"). Caraco neither complied with FDA's ruling by making a Paragraph IV certification nor challenged it under the APA, electing instead to maintain its section viii statement as to Claim 4. J.A. 342-68.

4. In a counterclaim filed on June 11, 2009—more than a year *after* its conversion to section viii—Caraco requested, "[u]nder 21 U.S.C. § 355(j)(5)(C)(ii)," an order "requiring [Novo] to correct the use code information submitted by [Novo]." J.A. 366 ¶ 97. Novo opposed on the ground that both the cause of action asserted and the relief sought were not authorized by that counterclaim provision, and because there is nothing to "correct" about the revised use code, which—as established by the unopposed declaration of Novo's FDA expert (*id.* at 414-33)—complies with all applicable regulations and directly tracks the FDA-mandated indication.[2]

a. Without any reference to the statutory text, the district court rejected Novo's position that the counterclaim was unauthorized (Pet. App. 95a-96a) and ordered Novo to "submi[t] to FDA an amended Form FDA 3542 that reinstates its former U-546 listing for Prandin and describes claim 4 of the '358 patent in section 4.2b as covering 'the use of rep-

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[2] Novo also argued that FDA was a necessary party because Caraco's challenge was (and still is) a collateral attack on FDA's administration of the Orange Book. *See* D.E. 373, at 10-11. To this day, FDA has not participated in these proceedings as a party or an *amicus*.

aglinide in combination with metformin to lower blood glucose.'" *Id.* at 65a-66a.

b. The Federal Circuit vacated the injunction. Pet. App. 1a-52a.

"[D]etect[ing] no ambiguity in the statutory language," the court held that "the Hatch-Waxman Act authorizes a counterclaim only if the listed patent does not claim any approved methods of using the listed drug." Pet. App. 12a. Because Caraco conceded that the listed patent "does claim an approved method of use" (J.A. 688-89), the counterclaim was not available to Caraco.

The court also held that "the terms of the counterclaim provision do not authorize an order compelling the patent holder to change its use code narrative." Pet. App. 14a-15a. That is because the counterclaim provision authorizes an order compelling the patentee "to correct or delete the patent information submitted ... under subsection (b) or (c)" (21 U.S.C. § 355(j)(5)(C)(ii)(I)), and "the Act defined the term 'patent information' as 'the patent number and the expiration date.'" Pet. App. 15a (citing *Valley Drug Co.* v. *Geneva Pharms. Inc.*, 344 F.3d 1294, 1296-97 (11th Cir. 2003)).

Judge Clevenger, who "agree[d] with Judge Rader's analysis of the relevant statutory provisions in this case and therefore join[ed] [his] opinion," wrote separately to emphasize that "Novo did nothing that was illegal or forbidden" and that "there is nothing illegal, or even incorrect, about Novo's current use code." Pet. App. 19a, 21a.

Judge Dyk dissented, arguing that "[a]n error in an Orange Book use code" should be "subject to correction" under the counterclaim provision. Pet. App.

43a; *see also id.* at 53a-64a (Gajarsa, J., dissenting from denial of rehearing) (similar).

5. Following the Federal Circuit's decision, proceedings on the remaining issues resumed in the district court.

Novo renewed its motion to dismiss for lack of subject-matter jurisdiction, arguing that Caraco's conversion from a Paragraph IV certification to a section viii statement defeated the jurisdictional basis for suit. The district court, however, denied that motion. Opp. App. 1a-10a.

On January 19, 2011, after a bench trial, the district court found Claim 4 invalid and unenforceable. Opp. App. 11a-106a. Novo's appeal from that judgment has been stayed pending the Court's decision in this case. *Novo Nordisk A/S* v. *Caraco Pharm. Labs., Ltd.*, No. 2011-1223 (Fed. Cir. July 27, 2011).

SUMMARY OF ARGUMENT

Caraco cannot even invoke, much less secure relief under, the Hatch-Waxman Act's counterclaim provision.

I. Caraco's conversion from a Paragraph IV certification to a section viii statement precludes the federal courts from entertaining the counterclaim.

A Paragraph IV certification is an act of patent infringement that vests the federal courts with jurisdiction (35 U.S.C. § 271(e)(2)(A)), and Congress limited the counterclaim to Paragraph IV suits. *See* 21 U.S.C. § 355(j)(5)(C)(ii). Caraco, however, withdrew its Paragraph IV certification with respect to the claim-in-suit in April 2008—more than a year *before* filing the counterclaim. Since then, it has proceeded under a section viii statement, which represents that there is no dispute regarding patent infringement. Caraco's conversion to section viii divested the feder-

al courts of jurisdiction over this lawsuit, including the subsequently filed counterclaim.

II. The Federal Circuit correctly construed the counterclaim, which requires the generic applicant to prove that "the patent does not claim ... an approved method of using the drug" and limits the remedy to "correct[ing] or delet[ing] the patent information submitted ... under subsection (b) or (c)." 21 U.S.C. § 355(j)(5)(C)(ii).

A. A patent either claims an approved use or it does not; the options are dichotomous. If the patent claims an approved use, then it may be listed in the Orange Book and the counterclaim is not available. Caraco's only response is to contend that "it can simultaneously be true that the patent *both* (1) 'claims an approved method of use' *and* 'does not claim an approved method of use'" (Caraco Br. 29-30), which is every bit as nonsensical as it sounds. FDA requires a "yes" or "no" answer to the question whether the patent claims an approved method; "both," as Caraco would have it, is not an option.

The statutory phrase "not ... an approved use" is equivalent to "no approved use"—the counterclaimant has the burden of proving that the listed patent does not claim *any* approved uses. This construction accords with both common sense and standard grammar. Caraco tries to avoid this conclusion by inverting the language of the statute—"the generic can point to 'an approved method' that the patent 'does not claim'" (Caraco Br. 29 (emphasis omitted))—so that the counterclaim would apply if the patent does not claim the singular use for which the generic applicant seeks carve-out approval. *Id.* at 27; *see also* U.S. Br. 15. But other provisions refer specifically to "a method of use patent which does not claim a use *for which the applicant is seeking approval*." 21 U.S.C. § 355(j)(2)(A)(viii) (emphasis add-

ed). Congress's decision not to draft the counterclaim similarly must be given effect.

A patent is properly listed in the Orange Book if it claims "a method of using such drug." 21 U.S.C. § 355(b)(1). Caraco concedes that this means *any* approved use, and affording the various provisions of the Hatch-Waxman Act a "complementary" reading (*Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661, 673 (1990)) requires interpreting the counterclaim's reference to "an approved use" in the same way.

The history and purpose of the counterclaim further confirm that it is available only if the patent does not claim any approved use. As Caraco acknowledges, the construction afforded the counterclaim by the court below fully addresses the problem that Congress set out to address. Additional adjustments to this complex regime are for Congress, not this Court, to implement. *See Microsoft Corp.* v. *AT&T Corp.*, 550 U.S. 437, 457 (2007). At bottom, the counterclaim is a delisting provision; if a patent is properly listed in the Orange Book, as Novo's patent concededly is, then the counterclaim is not available.

B. The counterclaim extends only to the "patent information submitted ... under subsection (b) or (c)" of Section 505; the referenced subsections, in turn, require submission (and publication) only of "the patent number and the expiration date." 21 U.S.C. § 355(b)(1), (c)(2). Contrary to Caraco's assertion, "patent information" does not include the use code narrative.

Caraco argues that "patent information" *also* includes anything else that FDA might by regulation require an innovative manufacturer to provide. That contention cannot be reconciled with the statutory text, which does not even hint that the "patent information submitted ... under" Section 505(b) and (c)

includes *non-statutory* submissions, or with the structure of the statute, which repeatedly uses "submitted under" to mean *statutory* patent information. Moreover, many other provisions expressly incorporate regulatory requirements; Congress's decision not to do so in the counterclaim must be respected.

The drafting history of the counterclaim conclusively refutes Caraco's argument. A predecessor bill would have expanded the statutorily required "patent information" to include a number of additional things, including "the approved use covered by the claim," and would have been broad enough to authorize a judicial action to "correct" this newly required information—the very relief Caraco seeks here. That bill, however, did not pass into law. Instead, pursuant to a much narrower legislative compromise, the counterclaim was limited to challenging the patent number and expiration date. Caraco is now asking this Court to adopt, by judicial fiat, that which Congress was unwilling or unable to enact.

III. Injunctive relief is not warranted because "there is nothing illegal, or even incorrect, about Novo's current use code." Pet. App. 21a (Clevenger, J., concurring).

Caraco's principal complaint is that Novo's use code narrative does not accurately describe the "scope" of Novo's patent. But a patent's scope is defined by its claims, and is subject to the detailed requirements of the Patent Act; the Hatch-Waxman Act does not require these intricacies to be boiled down to a 240-character entry on an FDA form. Rather, FDA itself recognizes that the use code narrative serves solely a notice function and is "not meant to substitute for the [ANDA] applicant's review of the patent and the approved labeling." 68 Fed. Reg. 36,676, 36,683 (June 18, 2003).

FDA has expressly authorized use code narratives based on "a description of each approved method of use *or indication*." 21 C.F.R. § 314.53(c)(2)(ii)(P)(1) (emphasis added). Novo has elected to base its use code narrative—for this patent, as for other listed patents in its portfolio—on the approved indication for the drug. This is consistent with FDA's guidance and, indeed, with use code narratives drafted by FDA itself. After all, FDA regulates *drugs*, including their labels (which must recite approved indications), not *patents*.

Caraco's objection to Novo's current use code narrative is really a collateral attack on FDA's longstanding decision to allow indication-based use codes. But that is not what the counterclaim is for. Rather, the appropriate avenue of judicial relief would have been a suit against FDA, in the appropriate forum, under the Administrative Procedure Act. Caraco elected not to pursue that course; as a result, all of its arguments that judicial review via the counterclaim is "necessary" ring hollow.

ARGUMENT

To prevail before this Court, Caraco must clear a series of obstacles, any one of which is sufficient to bar its counterclaim.

Caraco must establish the jurisdictional prerequisite to the counterclaim—a viable Paragraph IV dispute—even though it withdrew its Paragraph IV certification before filing the counterclaim. Caraco must satisfy the predicate for invoking the counterclaim—that the patent does not claim an approved method of using the drug at issue—even though it concedes that the patent does claim an approved method of using repaglinide. Caraco must fit itself within the counterclaim's remedial scope—which authorizes correction or deletion only of the patent number and expiration date—even though the use

code narrative is neither. And Caraco must demonstrate the need for judicial intervention—that is, that Novo's current use code narrative requires "correct[ion]"—even though that use code complies with all applicable rules.

Caraco cannot overcome any of these hurdles, much less *all* of them.

I. CARACO CANNOT PURSUE THE COUNTERCLAIM SINCE IT SWITCHED TO SECTION VIII

The Hatch-Waxman Act provides for jurisdiction in ANDA cases only if the generic applicant maintains a Paragraph IV certification with respect to the patent claim(s) at issue. *See Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661, 678 (1990); *see also* 35 U.S.C. § 271(e)(2)(A). The counterclaim, likewise, is available *only* in Paragraph IV litigation. *See* 21 U.S.C. § 355(j)(5)(C)(ii). Yet Caraco does not now have—and did not have at the time the counterclaim was filed—a Paragraph IV certification as to the sole patent claim at issue. Rather, Caraco amended its ANDA in April 2008 to assert only a section viii statement, thus depriving the federal courts of jurisdiction and destroying the statutory prerequisite for invoking the counterclaim.

An ANDA applicant may maintain either a Paragraph IV certification or a section viii statement as to a given patent claim, but not both. *Purepac Pharm. Co.* v. *Thompson*, 354 F.3d 877, 880 (D.C. Cir. 2004). A Paragraph IV certification is appropriate when an innovator's patent "claims a use" of the drug for which the ANDA filer seeks approval. 21 U.S.C. § 355(j)(2)(A)(vii). The ANDA applicant acknowledges the applicability of the patent, while certifying that it "is invalid or will not be infringed"

by the manufacture, use, or sale of the generic drug. *Id.* § 355(j)(2)(A)(vii)(IV). By contrast, a section viii statement asserts that the innovator's patent "does not claim a use" for which the ANDA filer seeks approval. *Id.* § 355(j)(2)(A)(viii). Paragraph IV certifications and section viii statements are thus mutually exclusive: "[E]ither the applicant is seeking approval for the use claimed in the patent, or it is not." *Purepac*, 354 F.3d at 880 (internal quotation marks omitted).

The choice between these two alternatives has significant consequences for federal jurisdiction. A Paragraph IV certification indicates the applicant's intent to sell a potentially infringing product and constitutes an "artificial act of infringement," thus "enabl[ing] the judicial adjudication" of claims for infringement and patent invalidity. *Eli Lilly*, 496 U.S. at 678; *see also* 35 U.S.C. § 271(e)(2)(A). In contrast, a section viii statement represents that there is no controversy between the parties regarding patent infringement. *Purepac*, 354 F.3d at 880; *see also* Colleen Kelly, *The Balance Between Innovation and Competition: The Hatch-Waxman Act, the 2003 Amendments, and Beyond*, 66 Food & Drug L.J. 417, 424 (2011) (section viii statement "does not constitute an act of infringement like a Paragraph IV certification").

The Hatch-Waxman counterclaim does not provide any freestanding basis for federal jurisdiction; it may be invoked only if the patent holder "brings a patent infringement action against the applicant." 21 U.S.C. § 355(j)(5)(C)(ii). The only such action that may be brought *before* FDA approves an ANDA is where a Paragraph IV certification has been made. 35 U.S.C. § 271(e)(2)(A). The jurisdictional basis for

the counterclaim is therefore coterminous with a Paragraph IV certification.

Congress expressly provided that the counterclaim provision "does not authorize the assertion" of the counterclaim "in any civil action or proceeding" *other than* a Paragraph IV lawsuit. 21 U.S.C. § 355(j)(5)(C)(ii)(II). In contrast to the original bill (S. 812), which would have permitted stand-alone challenges, the enacted provision reflects the legislative compromise to tie the counterclaim to Paragraph IV litigation. *See* H.R. Rep. No. 108-391, at 836 (2003) (Conf. Rep.) (counterclaim applies in "paragraph IV patent suit by an ANDA applicant seeking removal of a patent listed in the Orange Book").

Although Caraco originally filed a Paragraph IV certification with respect to Claim 4 of the '358 patent, initially creating jurisdiction for this lawsuit, it subsequently (in April 2008) amended its ANDA by withdrawing the Paragraph IV certification and replacing it with a section viii statement. J.A. 175. This amendment divested the federal courts of jurisdiction over any challenges involving Claim 4 of the '358 patent. *See Arizonans for Official English* v. *Arizona*, 520 U.S. 43, 67 (1997) (a justiciable controversy must exist at all stages of a lawsuit). Novo moved to dismiss on that basis. *See* D.E. 92, 478.

The district court recognized that "a section viii statement, unlike a Paragraph IV certification, does not constitute an act of infringement sufficient to invoke subject matter jurisdiction." Opp. App. 7a. It concluded, however, that Caraco "was pursuing *both* a paragraph IV certification *and* a section viii statement with respect to the '358 patent." *Id.* at 10a (emphases added). This ruling contravenes the controlling regulation, which provides that "[o]nce an

amendment ... is submitted, the application will no longer be considered to contain the prior certification." 21 C.F.R. § 314.94(a)(12)(viii). And the regulation accords with common sense: An ANDA filer logically cannot certify both that it is seeking approval for a use *not claimed* by an Orange-Book-listed patent (section viii) and that the same use *is claimed* by a listed patent that is invalid or not infringed (Paragraph IV). *See* 59 Fed. Reg. 50,338, 50,347 (Oct. 3, 1994). Thus, as the government explains (and Caraco does not dispute), "FDA does not ... permit a simultaneous paragraph IV certification and section viii statement to the same claim of a particular patent." U.S. Cert. Br. 8 n.1; *see also Purepac*, 354 F.3d at 880 ("patent ANDA applicants use either a paragraph IV certification or a section viii statement—they may not use both").

Since Caraco amended its ANDA in April 2008, more than a year *before* filing its counterclaim, there has been no case or controversy between Novo and Caraco within the meaning of Article III; Caraco's ANDA does not constitute an "artificial act of infringement" (*Eli Lilly*, 496 U.S. at 678) on which statutory jurisdiction could be predicated under 35 U.S.C. § 271(e)(2)(A); and there is therefore no "patent infringement suit" that could support a counterclaim under the 2003 amendments.[3]

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[3] The government has previously implied that, if a counterclaim were filed while there is a pending Paragraph IV certification, jurisdiction would not be lost by a *later* conversion to section viii. U.S. Cert. Br. 22. Assuming, *dubitante*, that could be right, here Caraco converted to section viii *before* filing the counterclaim. It is perhaps for this reason that the government's merits brief, like Caraco's, is silent on jurisdiction.

This result should not surprise. As Caraco itself acknowledges, section viii "is designed to avoid litigation." Caraco Br. 43. The counterclaim is *never* available if an ANDA applicant chooses to proceed under section viii rather than Paragraph IV, as Caraco did, because by definition there is no patent infringement litigation. *See* note 7, *infra*. Caraco's initiation and maintenance of the counterclaim, including in this Court, founders on that barrier—yet Caraco does not even address it.

II. THE FEDERAL CIRCUIT CORRECTLY CONSTRUED THE SCOPE OF THE COUNTERCLAIM

The Hatch-Waxman counterclaim provides that, if the ANDA applicant proves in a Paragraph IV lawsuit that "the patent does not claim ... an approved method of using the drug," then the court may order the NDA holder "to correct or delete the patent information submitted ... under subsection (b) or (c) of this section." 21 U.S.C. § 355(j)(5)(C)(ii).[4]

As the Federal Circuit correctly concluded, Caraco's attempt to invoke this counterclaim provision is foreclosed by the statutory language in two separate—and independently dispositive—respects. *First*, the counterclaim is unavailable where, as here, the patent-in-suit *does* claim "an approved method of using the drug." This is true even if the patent does not claim *all* approved methods. Pet. App. 11a-14a. *Second*, even where the counterclaim is available, the "patent information" subject to correction or deletion is limited to the patent number and expiration

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[4] The counterclaim and "complementary" provisions of Section 505 (*see Eli Lilly*, 496 U.S at 673) are excerpted in the statutory addendum, *infra*.

date, and thus does not include the use code narrative. *Id.* at 11a-16a.

A. The Counterclaim Is Not Available Where, As Here, The Patent Claims An Approved Method Of Use

The counterclaim provision requires the generic competitor to prove that the listed patent "does not claim ... an approved method of using the drug." 21 U.S.C. § 355(j)(5)(C)(ii); *see also* U.S. Br. 18-19. Caraco concedes, however, that Novo's patent "*does* claim an approved method of use." J.A. 688-89; *see also id.* at 396 (acknowledging that Novo's patent "covers an FDA-approved method of using the referenced drug"). The counterclaim is therefore unavailable.

1. A patent either "claim[s] an approved method" of using a particular drug, or it does not. This dichotomy is at the heart of the Hatch-Waxman Act's patent listing requirements, and was expressly adopted by Congress in the counterclaim. A patent that "claim[s] an approved method of use" for a drug cannot simultaneously be said "not [to] claim an approved method of use" for that drug; the two modes are dichotomous.

Caraco asserts that this straightforward reading of the statutory language "rests on a logical fallacy" because, in its view, "whether the patent claims an approved method of use" is not "necessarily an either-or-proposition." Caraco Br. 29. Indeed, an *essential* component of Caraco's argument is that "it can simultaneously be true that the patent *both* (1) 'claims an approved method of use' *and* (2) 'does not claim an approved method of use.'" *Id.* at 29-30. Nonsense. To be sure, as a matter of quantum mechanics, "[e]lementary particles can both exist and not exist at the same time." *Kusay* v. *United States*, 62 F.3d 192, 194 (7th Cir. 1995). But "[j]udicial pow-

er needs a more predictable basis" (*ibid.*), and patent claims, unlike Schrödinger's cat, cannot be in multiple, inconsistent states at once.

The language enacted by Congress means that the counterclaim is available only if "the listed patent does not claim *any*" (or, equivalently, claims *no*) "approved method of using the drug." Pet. App. 12a. Caraco protests that "Congress did not say 'any'; it said 'an.'" Caraco Br. 23. But what Congress *actually* said was "not ... an." As the Federal Circuit correctly recognized, "[w]hen an indefinite article is preceded and qualified by a negative, standard grammar generally provides that [it] means 'any.'" Pet. App. 12a. That is because the construction "not ... an" equates to "none." *Shorter Oxford English Dictionary* (5th ed. 2002) (defining "an" with a "preceding negative" to mean "none at all of, no—of any kind; not even one"); *see also, e.g.*, *American Heritage Dictionary of the English Language* 1 (4th ed. 2000) ("not a drop to drink"). Contemporaneous dictionaries consistently include this definition of "a" or "an" in the context of a negative formulation.[5] While Caraco dismisses these as "secondary definitions" (Caraco Br. 26), they are the *only* definitions applicable where, as here, the article is preceded and qualified by a negative ("does not claim"), and Caraco does not cite a single definition or other authority

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[5] *See, e.g.*, *Random House Webster's Unabridged Dictionary* (2d ed. 2001) ("any; a single: not a one"); *Oxford American College Dictionary* (2002) ("[with negative] one single; any: I haven't a thing to wear"); *Microsoft Encarta College Dictionary* (2001) ("ANY used in negative structures to emphasize a complete absence of something," as in "He doesn't have a hope!"); *Webster's II New Collegiate Dictionary* (3d ed. 2005) ("Any < not a bite to eat>"); *Oxford American Dictionary and Thesaurus with Language Guide* (2003) ("one single (not a thing in sight)").

that disagrees with this construction or states a contrary rule.

Caraco, implicitly acknowledging that it cannot satisfy the statutory requirement as written, is forced to concoct strained (and irrelevant) hypotheticals. *See* Caraco Br. 26-28; *see also* U.S. Br. 22 n.2 (same). They serve only to confirm that, on Caraco's reading, an ANDA applicant may invoke the counterclaim if it can identify *any* "'approved method' that the patent 'does not claim.'" Caraco Br. 29 (emphasis omitted). That would bring the counterclaim into play unless the patent claimed "*all* approved methods" of use. Pet. App. 12a. The statute, however, says no such thing.

To make its proposed construction work, Caraco has to invert the statutory language: According to Caraco, the counterclaim is available if "the generic can point to 'an approved method' that the patent 'does not claim.'" Caraco Br. 29 (emphasis omitted). This inversion, however, requires substituting a definite article ("the") for the indefinite article ("an") that Congress actually used. As Caraco admits, it reads the statute as referring to "a single approved method of using the drug"—that is, *the* "*particular* approved method of use" invoked by the ANDA filer. *Id.* at 27 (emphasis added). Caraco repeatedly reminds the Court that "[c]hang[ing] an 'an' to a 'the' ... go[es] from huge savings to huge cost." *Examining the Senate and House Versions of the "Greater Access to Affordable Pharmaceuticals Act": Hearing Before the Senate Comm. on the Judiciary*, 108th Cong. 119 (2003) (Sen. Schumer). But that is *precisely* what Caraco is attempting to do.

The government, for its part, claims that the relevant statutory inquiry is whether the patent "does not claim ... *the approved use* for which [the generic company] seeks carve-out labeling under section

viii." U.S. Br. 15 (emphasis added). As with Caraco's formulation, the government would impermissibly convert the article from indefinite to definite. Moreover, where Congress intended to impose additional limitations or qualifications on "approved use," it did so expressly. Thus, section viii statements are appropriate only "[i]f ... information was filed under subsection (b) or (c) of this section for a method of use patent which does not claim a use *for which the applicant is seeking approval*." 21 U.S.C. § 355(j)(2)(A)(viii) (emphasis added).[6] Congress's decision to include such "language in one section of a statute but omi[t] it" elsewhere must be presumed "intentiona[l] and purpose[ful]." *Bates* v. *United States*, 522 U.S. 23, 29-30 (1997). And adding the language to a provision "from which it is conspicuously absent," of course, "more closely resembles inventing a statute rather than interpreting one." *Hardt* v. *Reliance Standard Life Ins. Co.*, 130 S. Ct. 2149, 2156 (2010) (internal quotation marks omitted).

2. The Federal Circuit's interpretation of the counterclaim provision is also consistent with this Court's requirement that the Hatch-Waxman Act be "taken as a whole." *Eli Lilly*, 496 U.S. at 669. The Hatch-Waxman Act requires listing of patents that

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[6] FDA interprets "does not claim a use" in this provision as referring to *any* use covered by the patent. *See* 21 C.F.R. § 314.94(a)(12)(iii)(A) (allowing section viii statement if "the labeling for the drug product for which the applicant is seeking approval does not include *any* indications that are covered by the use patent" and requiring "a statement explaining that the method of use patent does not claim *any* of the proposed indications" (emphases added)). Caraco does not explain why the same construction should not be applied to the counterclaim's similar language.

claim "a method of using such drug" (21 U.S.C. § 355(b)(1)), and the counterclaim is available if the owner of a patent "for the drug ... a use of which is claimed by the patent" initiates an infringement action (*id.* § 355(j)(5)(C)(ii)(I)). In both instances it is clear from context that the indefinite article "a" means any—as Caraco has previously admitted. Pet. C.A. Br. 38 n.2 ("an NDA holder may list a patent if it covers any approved use"). Reading "an approved method" the same way is the only way to harmonize the statute as a whole. *See, e.g.*, *Powerex Corp.* v. *Reliant Energy Servs., Inc.*, 551 U.S. 224, 232 (2007) ("identical words and phrases within the same statute should normally be given the same meaning").

The Hatch-Waxman Act's listing provisions provide a particularly compelling parallel with the counterclaim. For a method-of-use patent to be properly listed in the Orange Book, it must "clai[m] ... a method of using such drug." 21 U.S.C. § 355(b)(1). An Orange Book listing is improper, therefore, if the patent *does not* "clai[m] ... a method of using such drug." Thus, the counterclaim provision operates to remove from the Orange Book those method-of-use patents that were not properly listed in the first place, and puts the burden on the counterclaimant to prove that the listing is improper. *See* Caraco Br. 29 (acknowledging that the generic company "bears the burden of proof under the statute"). A patent is either correctly listed in the Orange Book or it is not—as with the counterclaim provision, the listing requirement turns on the dichotomy between patents that "claim ... an approved method of use" and those that do not. It *is* an either-or proposition.

This is, moreover, how the listing requirements have consistently been applied by FDA. Form 3542 asks simply: "Does the patent ... claim an approved method of use of the approved drug product?" J.A. 98. There are only two possible answers to this ques-

tion: "Yes" and "No." *Ibid.* Dichotomous again. The patent holder cannot answer, as Caraco's theory would require, "Both" (or "Yes, but not all"). And if the patent holder checks "No," then the patent cannot be listed in the Orange Book at all. *Id.* at 99.

Eli Lilly—this Court's only previous foray into the wilds of the Hatch-Waxman Act—recognized that the Act's provisions should be construed in a "complementary" manner. 496 U.S. at 673. Contrary to Caraco's assertion (at 42-45), this does not mean that the counterclaim should be harmonized with section viii; the counterclaim has *nothing to do* with section viii.[7] Rather, the complementariness principle demands that the counterclaim be construed in parallel with the listing requirements of Section 505(b) and (c)—which, unlike section viii, are actually cross-referenced in the counterclaim itself.

As Caraco concedes, Novo's patent was properly listed in the Orange Book because it "[d]oes ... claim an approved method of use of the approved drug product." J.A. 98; *see also id.* at 396 (Caraco's concession that the '358 patent is "properly listed in the Orange Book"). Accordingly, Caraco's assertion that, for purposes of the counterclaim provision, the patent "does not claim ... an approved method of us[e]"

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[7] Caraco's suggestion that "Section viii and the counterclaim were meant generally to be complementary" (Caraco Br. 47 (internal quotation marks omitted)), like the government's view that the counterclaim "facilitate[s] the section viii process" (U.S. Br. 21), overlooks that the statute makes them mutually exclusive: If an ANDA applicant elects to proceed through section viii, the counterclaim is categorically unavailable. Consequently, Caraco's lament that the decision below "eviscerate[s]" section viii (Caraco Br. 41) is meaningless.

(21 U.S.C. § 355(j)(5)(C)(ii)) is at war with the statutory scheme.

3. The drafting history of the counterclaim further confirms that it is unavailable here. The counterclaim was enacted to "correct the specific issue raised" in *Mylan Pharmaceuticals, Inc.* v. *Thompson*, 268 F.3d 1323 (Fed. Cir. 2001)—that is, "to deter pioneering manufacturers from listing patents that were not related at all to the patented product or method." Pet. App. 13a.

a. In *Mylan*, the Federal Circuit held that a generic competitor could not seek a court order requiring a patentee to delist an improperly listed patent because it "did not claim ... an approved method of using [the drug]." 268 F.3d at 1331. Because a delisting cause of action was not explicitly authorized by the Hatch-Waxman Act, the court reasoned that Mylan's suit was "an impermissible attempt by a private party to enforce the FDCA." *Id.* at 1329-30 (citing *Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341 (2001)). Congress responded with the counterclaim, which (echoing the language of *Mylan*) is available only where "the patent does not claim ... an approved method of using the drug." 21 U.S.C. § 355(j)(5)(C)(ii)(I)(bb); *see also* Pet. App. 21a (Clevenger, J., concurring) ("The counterclaim statute ... was designed to cure the situation presented in *Mylan*").

Caraco concedes that the Federal Circuit's interpretation of the counterclaim fully accounts for "the problem in the *Mylan* case." Caraco Br. 31. It claims, however, that the counterclaim was designed to remedy a broader range of "improper Orange Book listings" and that "[t]he legislative history contains no significant discussion of *Mylan*." *Id.* at 31-32. This grossly mischaracterizes the historical record.

In the debates leading to enactment of the counterclaim provision, Members of Congress were focused on several publicized instances of perceived abuse. *See* Kelly, *supra*, at 435-39 (summarizing legislative background). As the initial patent for a drug's active ingredient neared expiration, and after the generic had filed its ANDA and certified to the patents previously listed in the Orange Book for a particular drug, some branded companies would list one or more additional patents in the Orange Book related to relatively minor aspects of the underlying drug—such as, for example, "the color or the design of the packaging or the scoring of the pill that really did not indicate a different or improved use for the product." 148 Cong. Rec. S6844 (July 16, 2002) (Sen. Collins). Whether these late-listed, additional patents actually claimed the approved drug or an approved use of the drug was questionable, but their inclusion in the Orange Book would nonetheless require the ANDA applicant to provide a Paragraph IV certification that would lead to a 30-month stay. And because, at that time, there was no limit on the number of 30-month stays, some branded companies could take advantage of this strategy indefinitely—thus "evergreening" their patents. *Id.* at S6828-29 (Sen. Kennedy).

According to several legislators, the *Mylan* litigation exemplified this perceived abuse. *See*, *e.g.*, 148 Cong. Rec. S7637 (July 31, 2002) (Sen. Schumer) ("Problems caused by th[e] [multiple 30-month stay] provision are illustrated by the facts of the Buspar litigation"); 148 Cong. Rec. S7344 (July 25, 2002) (Sen. Hatch) ("We all know of the now infamous case of the drug, Buspar"). The NDA holder owned an Orange-Book-listed patent for BuSpar, an FDA-approved anti-anxiety medication that contained the ingredient buspirone. 268 F.3d at 1327. Hours before the BuSpar patent expired, the branded compa-

ny submitted to FDA a new patent, which claimed a process for treating anxiety by introducing an active metabolite of buspirone into the body. *Id.* at 1328. This patent was not properly listed because it claimed only a metabolite of buspirone rather than the drug itself. *Ibid.* But existing law, the Federal Circuit held, did not provide Mylan with any opportunity to seek a judicial order delisting the patent on the ground that it "did not claim ... an approved method of using [the drug]." *Id.* at 1331.

Congress's primary response to *Mylan* and like cases was to reform the 30-month stay provision, eliminating repeated stays with respect to the same drug. *See* 21 U.S.C. § 355(j)(5)(B). Congress also adopted a narrow counterclaim provision to address the specific problem in *Mylan*: patents that should never have been listed in the Orange Book.

Caraco suggests, erroneously, that the "'abusive practices in the pharmaceutical industry'" addressed by Congress included use code narratives. Caraco Br. 10 (quoting 149 Cong. Rec. S15,745 (Nov. 24, 2003) (Sen. Schumer)). According to Caraco, for instance, "FDA ... urged that, to resolve problems with the scope of patent use codes, 'the courts are the appropriate mechanism.'" *Id.* at 32 (quoting 68 Fed. Reg. 36,676, 36,683 (June 18, 2003)). What FDA *actually* said was that "[a] fundamental assumption of the Hatch-Waxman Amendments is that the courts are the appropriate mechanism *for the resolution of disputes about the scope and validity of patents*." 68 Fed. Reg. at 36,683 (emphasis added). Similarly, although Caraco implies (at 33) that Senator Gregg's reference to "those issues" (149 Cong. Rec. S8193 (June 19, 2003)) had something to do with use code narratives, he was instead referring to "interminable [30-month] stays" and *generic* companies "tak[ing] advantage of the 180-day exclusivity clause"—both of which were "addresse[d] ... very conscientiously" by

the statute. *Ibid.* No Member of Congress *ever* discussed use code narratives in connection with the 2003 amendments, and Caraco's contrary suggestion is unadulterated revisionism.

Indeed, until August 2003, FDA *itself* wrote use code narratives. *See* 68 Fed. Reg. at 36,683. Neither Caraco nor the government explains how, when Congress passed the counterclaim provision in June 2003, it could have intended to "combat" a "sort of manipulation"—*i.e.*, "submitting to FDA an overbroad description of [a] method-of-use patent" (U.S. Br. 17)—that was not even *possible*. Again, neither the statute nor the legislative history contains even a *single* reference to the issue of use code narratives; Congress was, instead, focused on improperly listed patents, and the solution it adopted was narrowly tailored to solve that specific problem.

Caraco would prefer that Congress have adopted a broader provision that addressed other purported (but unidentified) "abuses," but this is nothing more than a policy-based plea to extend the counterclaim beyond the *Mylan* situation that Congress set out to address—and, indeed, to resurrect a bill that Congress was unwilling or unable to pass. If the counterclaim is to be extended beyond *Mylan*, then such an extension is a task for Congress, not this Court. *See Microsoft Corp.* v. *AT&T Corp.*, 550 U.S. 437, 457 (2007) (any such "'loophole' ... is properly left for Congress to consider, and to close if it finds such action warranted"); *see also 62 Cases of Jam* v. *United States*, 340 U.S. 593, 600 (1951).

b. Caraco contends, however, that reading the counterclaim provision as limited to the *Mylan* situation would "'render superfluous' the term 'correct.'" Pet. 32 (citing *Astoria Fed. Sav. & Loan Ass'n* v. *Solimino*, 501 U.S. 104, 112 (1991)). Not so: If a patent is improperly listed because it does not claim an ap-

proved method of using the drug, then the court may order *either* delisting *or* correction of the statutory patent information.

In most cases in which a generic competitor proves that the listed patent does not claim an approved method, the appropriate remedy will be delisting. But if an error were made in listing a patent—for example, the wrong patent number were submitted—the Hatch-Waxman counterclaim authorizes the court to order correction of the statutory patent information without requiring a resubmission by the NDA holder. This could have important consequences (including benefits for generic challengers) under the various stay provisions of the Act. *See* Kelly, *supra*, at 446-50.

Moreover, even if the statutory term "correc[t]" has little or no independent work to do under the Federal Circuit's reading of the counterclaim, this Court should not distort the remainder of the statute to accommodate that single word. "Surplusage does not always produce ambiguity," and this Court's "preference for avoiding surplusage constructions is not absolute." *Lamie* v. *U.S. Trustee*, 540 U.S. 526, 536 (2004); *see also Chickasaw Nation* v. *United States*, 534 U.S. 84, 94 (2001).

The statutory term "correct" is an artifact of the earlier, failed bills that would have required submission of a much broader range of "patent information" and permitted a suit to correct that information. S. 812, 107th Cong. § 103(a)(2)(C), (E) (2002). When Congress eliminated the submission requirements to achieve legislative consensus, it modified the counterclaim provision by adding the word "correct" to the "delete" clause. At the same time, Congress confirmed its understanding that the counterclaim is—primarily, if not exclusively—a delisting provision. *See* H.R. Rep. No. 108-391, at 836 (counterclaim

available to "ANDA applicant *seeking removal* of a patent listed in the Orange Book" (emphasis added)).

Where, as here, the patent is properly listed, the counterclaim never comes into play. There is nothing to delete—or correct.

B. The Counterclaim Does Not Reach Use Code Narratives

Caraco seeks a judicial order requiring Novo to withdraw its current use code narrative and replace it with one selected by Caraco. Even if the Hatch-Waxman counterclaim were available, however, it would not allow the remedy sought by Caraco. Rather, the only remedy authorized by statute is correcting or deleting the "patent information submitted by the [patent] holder under subsection (b) or (c)" of Section 505. 21 U.S.C. § 355(j)(5)(C)(ii)(I). The only such "patent information" is "the patent number and the expiration date of any patent" covering the drug or a method of use. *Id.* § 355(b)(1), (c)(2). It does not extend to the use code narrative.

1. Section 505(b) requires NDA filers to submit "the *patent number* and the *expiration date* of any patent which claims the drug ... or which claims a method of using such drug" and directs the Secretary to "publish [the] *information submitted under*" this clause. 21 U.S.C. § 355(b)(1) (emphases added). Section 505(c) states that "[i]f the *patent information* described in subsection (b) of this section could not be filed with the submission of an application," the holder of an approved application "shall file with the Secretary the *patent number* and the *expiration date* of any patent which claims the drug ... or which claims a method of using such drug." *Id.* § 355(c)(2) (emphases added).

Section 505 therefore makes clear that the "patent information" submitted under subsection (b) or

(c)—the very phrase used in the counterclaim provision—is limited to the patent number and expiration date. *See IBP, Inc.* v. *Alvarez*, 546 U.S. 21, 34 (2005) (applying "the normal rule of statutory interpretation that identical words used in different parts of the same statute are generally presumed to have the same meaning").

Caraco wants to rewrite the statute, arguing that the "patent information submitted by the holder under subsection (b) or (c)" really means any "patent information submitted under FDA regulations." Caraco Br. 35; *see also* U.S. Br. 24 ("[p]atent information" subject to the counterclaim "includes everything FDA requires NDA holders to submit"). But the only textual hook it asserts is that the counterclaim "says 'submitted ... under'" rather than "'specified in' or 'described in.'" Caraco Br. 34; *see also* U.S. Br. 24. This distinction is perfectly understandable; after all, the counterclaim is referring to the content of a patent holder's *submission* to FDA, whereas the provisions using "specified in" or "described in" involve information that has not been "submitted."[8] But it is, in any event, a distinction without a difference: The counterclaim refers to information "submitted ... under" two specific provisions, each of which provides for submission only of the patent

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[8] Section 505(c)(2) refers to "patent information described in subsection (b)," for instance, because that provision is triggered only if the information "could *not* be filed with the submission of an application under subsection (b) of this section." 21 U.S.C. § 355(c)(2) (emphasis added). Similarly, Section 505(d)(6) discusses the statutory remedy "[i]f the Secretary finds ... the application *failed* to contain the patent information prescribed by subsection (b)." *Id.* § 355(d)(6) (emphasis added); *see also id.* § 355(e)(4) ("the patent information prescribed by subsection (c) of this section was not filed within thirty days").

number and expiration date—and not other information, even if required by FDA regulation. *See, e.g.*, 21 C.F.R. § 314.53(c)(2)(ii)(J) (requiring NDA holders to provide e-mail addresses for agents or representatives); Pet. App. 211a (same).

Nor is Caraco correct that other provisions of the Hatch-Waxman Act "us[e] the phrase 'submitted under' ... when referring to patent information submitted under FDA regulations." Caraco Br. 35 (citing 21 U.S.C. § 355(c)(2), (j)(5)(D)(i)(I)(bb)(CC)). In both of the examples it cites, as in the counterclaim provision at issue here, the statute says absolutely nothing about FDA regulations.

One of Caraco's examples provides for forfeiture of the exclusivity period otherwise available to the first generic company to file a Paragraph IV certification if that company fails to market its drug within 75 days after "[t]he patent information submitted under subsection (b) or (c) of this section is withdrawn by the holder of the application approved under subsection (b) of this section." 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)(CC). There is no basis in the text of this provision to interpret it as referring to any information other than patent number and expiration date. (Otherwise, the NDA holder could precipitate a forfeiture merely by "withdraw[ing]" the e-mail address of its agent or representative.) To the contrary, the provision is designed to avoid delay by the generic applicant after removal of the patent from the Orange Book *altogether*.

Caraco's other example provides that, "[u]pon the submission of patent information under this subsection, the Secretary shall publish it." 21 U.S.C. § 355(c)(2). But Caraco provides no reason to believe that this publication requirement extends to whatever additional information FDA chooses to require by regulation; indeed, such an interpretation would

mean, implausibly, that FDA would be in violation of its *statutory* obligations if it were by *regulation* to require, but then decline to publish, information (such as the e-mail addresses of agents or representatives—which FDA does not in fact publish). The proper view is that FDA "publishes th[e] patent information" submitted under Section 505(b) and (c) "along with *other information* about the drug." *Valley Drug Co.* v. *Geneva Pharms., Inc.*, 344 F.3d 1294, 1297 (11th Cir. 2003) (emphasis added).

Indeed, Caraco's wishful reading of "submitted under" is refuted by Section 505(b) itself. After requiring submission of the patent number and expiration date, Section 505(b)(1)(G) provides that, "[u]pon approval of the [NDA], the Secretary shall publish information *submitted under the two preceding sentences*." 21 U.S.C. § 355(b)(1)(G) (emphasis added). This narrow reference to the "two preceding sentences" cannot reasonably be read to incorporate the full range of information that FDA has elected to request (including e-mail addresses), rather than the specific patent information identified in those "two preceding sentences." And FDA *itself* has explained that "[t]he statute and regulation require the NDA holder to submit, and in turn FDA to publish, only the patent number and expiration date." FDA Br. 16, *Teva Pharms. USA Inc.* v. *Leavitt*, No. 08-5141 (D.C. Cir. June 18, 2008). Caraco's interpretation of "submitted under" conflicts with the agency's own.[9]

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[9] Caraco's reliance on *Ardestani* v. *INS*, 502 U.S. 129 (1991), is misplaced. The Court did not hold, as Caraco claims, that "'under,' followed by a statutory provision" necessarily "refers to regulatory proceedings subject to, or governed by, that provision." Caraco Br. 35-36. On the contrary, this Court recognized that "[t]he word 'under' has many dictionary definitions and

The remainder of the statute shows that Congress knows perfectly well how to invoke FDA's implementing regulations when it so wishes. In Section 505(q), for instance, Congress provided that ANDA approval may be delayed when a citizen petition is "submitted to the Secretary pursuant to section 10.30 or 10.35 of title 21, Code of Federal Regulations (or any successor regulations)." 21 U.S.C. § 355(q); *see also id.* § 355(i), (k), (o) (referring to regulations as establishing standard of conduct). And even where Congress did not include chapter and verse, it nonetheless understood how to incorporate regulatory (as opposed to statutory) requirements. *See id.* § 343(r)(2)(A)(i) (providing that certain nutrient claims "may be made only if the characterization of the level made in the claim uses terms which are defined in regulations of the Secretary"); *see also, e.g., id.* §§ 352n, 354(b), 356a(c). Indeed, the FDCA contains *more than 100* express references to FDA regulations.

But even though—as Caraco repeatedly reminds the Court—FDA had long "required brands to submit more than patent numbers and expiries" (Caraco Br. 40 n.11), Congress did not even hint *in the counterclaim* that it was referring to those regulations, let alone expressly invoke them. *See Kucana* v. *Holder*, 130 S. Ct. 827, 837 (2010) ("If Congress wanted the jurisdictional bar to encompass decisions specified as discretionary by regulation along with those made discretionary by statute, ... Congress could easily have said so").

[Footnote continued from previous page]

must draw its meaning from its context." 502 U.S. at 135. The context here has nothing to do with FDA regulations.

2. Even if the statutory text and structure were otherwise open to Caraco's interpretation, the drafting history conclusively forecloses the theory that "submitted ... under subsection (b) or (c)" includes FDA's regulatory requirements. Indeed, Caraco is attempting to obtain through judicial reimagination of the counterclaim provision a result that Congress considered but declined to adopt.

a. Before Congress passed the counterclaim provision at issue here, it considered several proposals that would have required NDA holders to provide an expanded list of statutory patent information, including, "if the patent claims a method of use, the approved use covered by the claim." S. 812, 107th Cong. § 103(a)(2)(C)(iv) (2002). And the generic company would have been permitted to "bring a civil action ... seeking an order requiring that the holder of the application amend the application ... to correct patent information filed" under the expanded submission requirements. *Id.* § 103(a)(2)(E).

These bills would have been broad enough to authorize what Caraco seeks here: a judicial challenge to the use code narrative. But the backers of such a right (including Representative Waxman) lacked sufficient votes to move it through Congress—at least seven bills containing this provision failed to pass. The ensuing legislative compromise explains why the counterclaim provision, as enacted, is far narrower than any of these earlier bills. Yet Caraco and all of its *amici*, including the United States, fail even to inform the Court of these predecessor bills, let alone attempt to analyze their impact on the issues before the Court.

Simply put, Caraco's interpretation of the counterclaim provision "would effectively resurrect the scheme rejected by Congress." *Smith* v. *United States*, 507 U.S. 197, 203 n.4 (1993). Yet Congress's

"rejection of the very language that would have achieved the result" urged by Caraco "weighs heavily against [that] interpretation." *Hamdan* v. *Rumsfeld*, 548 U.S. 557, 579-80 (2006); *see also*, *e.g.*, *Doe* v. *Chao*, 540 U.S. 614, 622-23 (2004) (same). Indeed, "[f]ew principles of statutory construction are more compelling than the proposition that Congress does not intend *sub silentio* to enact statutory language that it has earlier discarded in favor of other language." *INS* v. *Cardoza-Fonseca*, 480 U.S. 421, 442-43 (1987).

In this case, the drafting history of the counterclaim provision provides an "unusually clear indication" (*Thompson* v. *Thompson*, 484 U.S. 174, 183-84 (1988)) that Congress did not intend the enacted provision to reach things, including use code narratives, that Congress declined to require by statute.

b. The drafting history is also a complete answer to Caraco's speculation that, since FDA revised its Form 3542 regulation a few months before the counterclaim was enacted, Congress "must" have intended the counterclaim to reach the requirements of the new form. Caraco Br. 39-41. Since Congress declined to impose these requirements directly, it is ludicrous to suggest that the same Congress did so indirectly.

According to Caraco, "FDA explained" that "its 'principal legal authority for the final rule [revising Form 3542] is section 505 of the act'—in particular, 'the patent submission ... requirements' of 'Section 505(b) and (c).'" Caraco Br. 36 (quoting 68 Fed. Reg. at 36,697-98). What FDA *actually* said is simply: "Section 505(b) and (c) of the act describes the contents of an NDA and 505(b)(2) application, including the patent submission and patent certification requirements." 68 Fed. Reg. at 36,698. Elsewhere in the final rule FDA acknowledged the limited scope of

those subsections. *Id.* at 36,676. In fact, FDA's authority to promulgate regulations is found in another provision of the FDCA. 21 U.S.C. § 371(a).

When later challenged on its authority to require NDA holders to provide a use code narrative, FDA did *not* reference the pertinent parts of subsections (b) or (c); rather, it described the submission of use code narratives as a "regulatory requirement" that "provides for effective implementation of the patent certification and 'section viii statement' provisions" in subsection (j). 72 Fed. Reg. 21,266, 21,268-69 (Apr. 30, 2007). Because FDA has expressly disclaimed that its Form 3542 requirements rest on a construction of the statutory term "patent information," Caraco's plea for deference (Caraco Br. 38) is so baseless that not even the Solicitor General—typically quick to defend the prerogatives of client agencies—invokes deference in this case.

FDA's regulation requiring the submission of use code narratives, among other information, was offered as an *alternative* to the proposed legislation that could not pass the House. As part of the legislative compromise, the executive branch agreed to require additional information from NDA holders. But as part of that same compromise, the legislative branch agreed not to make that same information statutorily required or subject to the counterclaim. The judicial branch, of course, has no warrant to upset that compromise—yet that is precisely what Caraco is asking this Court to do.

III. Caraco Is Not Entitled To An Order Compelling Novo To Change Its Use Code Narrative

Even if Caraco could invoke the counterclaim, the injunction it seeks would be inappropriate. *First*, because Novo's use code narrative is fully compliant with all regulatory requirements, there is nothing to

"correct" under the counterclaim provision. *See* Pet. App. 21a (Clevenger, J., concurring) ("there is nothing illegal, or even incorrect, about Novo's current use code"). *Second*, although the relief afforded by the counterclaim is discretionary, Caraco has never even attempted to satisfy the traditional four-factor test for injunctive relief. *See eBay Inc.* v. *Merc Exchange, L.L.C.*, 547 U.S. 388, 391 (2006).

A. Novo's Current Use Code Narrative Is "Correct"

The counterclaim authorizes courts to order the "correct[ion] or delet[ion]" of statutorily submitted patent information. 21 U.S.C. § 355(j)(5)(C)(ii)(I). Caraco does not seek the "delet[ion]" of Novo's patent from the Orange Book but instead claims that the use code narrative should be "correct[ed]." Caraco Br. 48-49. Caraco's request must fail because it cannot establish that Novo's existing narrative is *in*correct.

1. Caraco makes the assumption—repeated almost 20 times in its brief—that the use code narrative must "describe the patent's scope, so FDA and generics can determine whether infringing uses may be carved out from the generic's labeling." Caraco Br. 50; *see also* GPhA Br. 26 ("the NDA applicant [must] tailor its use code to correspond to the legitimate scope of the patent"); U.S. Br. 22 (criticizing "disparit[ies] between the NDA holder's use code and the patent's actual coverage"). That assumption, however, is not just unsupported, but flat wrong.

The patent itself—not the use code narrative—"must describe the exact scope of an invention." *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 373 (1996). The precise boundaries of patent claims, which this Court has "likened to the description in a deed" (*Motion Picture Patents Co.* v. *Universal Film Mfg. Co.*, 243 U.S. 502, 510 (1917)), are de-

fined by a complicated series of rules. *See* 35 U.S.C. §§ 101-103, 112; *see also* Manual of Patent Examining Procedure § 608.01(l)-(n). Moreover, "claims are to be construed in the light of the specifications" (*United States* v. *Adams*, 383 U.S. 39, 49 (1966)) and "with reference to the file wrapper or prosecution history in the Patent Office" (*Graham* v. *John Deere Co.*, 383 U.S. 1, 33 (1966)), and the "patent's scope is not limited to its literal terms, but embraces all equivalents to the claims described." *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 723 (2002). These nuances, and many more, are governed by a different statute (the Patent Act) and overseen by a different agency (the Patent and Trademark Office).

The Hatch-Waxman Act does not create a junior-varsity patent system in which all of these intricacies must be distilled down to a 240-character "tweet" in an FDA database. Rather, FDA's requirement of a use code narrative is simply "intended to alert ANDA ... applicants to the existence of a patent that claims an approved use." 68 Fed. Reg. at 36,683. As FDA has emphasized, it is "not meant to substitute for the applicant's review of the patent and the approved labeling." *Ibid.* And there is no dispute that Caraco is fully apprised of the scope of the '358 patent, as claimed in the patent itself. *See, e.g.*, J.A. 322, 338-39 (Caraco's arguments on patent scope).

For this reason, it is unsurprising that FDA has *never* required the use code narrative to replicate the "approved method[s] of using the drug" covered by the patent, as Caraco maintains. Caraco Br. 49-50. The relevant regulation requires applicants to provide "a description of each approved method of use *or indication*." 21 C.F.R. § 314.53(c)(2)(ii)(P)(1) (emphasis added); *see also* 59 Fed. Reg. at 50,346 ("for a use patent, FDA includes in the Orange Book a code identifying the indication covered by the patent").

Similarly, Form 3542 itself permits NDA holders to "[s]ubmit the description of the approved *indication* or method of use that you propose FDA include as the 'Use Code' in the Orange Book." Pet. App. 213a (emphasis added).

FDA's guidance is expressly written in the alternative: An applicant may describe *either* the indication *or* the method of use. *See, e.g.*, *Garcia* v. *United States*, 469 U.S. 70, 73 (1984) ("terms connected in the disjunctive" must "be given separate meanings"). A use code that tracks the approved indication thus complies with the FDA's own regulation and instructions. *See* J.A. 424 ¶ 29.

FDA's decision to permit use code narratives based on approved indications makes perfect sense considering that FDA regulates *drugs*, not *patents*. The central focus of its regulatory oversight is to determine whether a drug or method is safe and effective for the treatment of a particular disease or condition. Prescription drug labels must contain an "indications" section stating that the drug (or a use of the drug) is "indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition." 21 C.F.R. § 201.57(c)(2). FDA's focus on indications is entirely consistent with the statutory scheme—including section viii carve-outs. *See* H.R. Rep. No. 98-857, Part I, at 21 (1984) ("The [ANDA] applicant need not seek approval for all of the *indications* for which the listed drug has been approved" (emphasis added)). Unsurprisingly, no court has *ever* rejected or disapproved a use code narrative that incorporates an FDA-approved indication.

2. It is undisputed that Novo's current use code narrative ("[a] method for improving glycemic control in adults with type 2 diabetes mellitus") correctly recites the approved indication for the drug

("PRANDIN is indicated ... to improve glycemic control in adults with type 2 diabetes mellitus")—an indication required by FDA in its 2007 directive. All of the listed patents in Novo's portfolio have indication-based use code narratives, and Novo's amendment of the PRANDIN® narrative comports with that corporate practice.

Moreover, Novo's use code narrative is consistent with the one created for PRANDIN® by FDA itself. In 1997, when repaglinide was first approved, there were two approved methods of use for PRANDIN®: use in monotherapy and use in combination therapy with metformin. FDA's use code (U-214) did not distinguish between the two approved uses, nor did it define the scope of the patent then at issue (U.S. Patent No. 5,312,924). Rather, the U-214 use code narrative stated: "Use as a blood glucose-lowering agent." J.A. 425 ¶ 34. If this indication-based use code created by FDA was proper (and here *is* an appropriate place for deference), then Novo's current use code narrative must be proper as well.[10]

"FDA will not list the patent in the Orange Book [if] the [use code] information requested ... is not provided in full." Pet. App. 213a; *see also* 21 C.F.R. § 314.53(c)(2)(ii) (FDA may "notify an applicant that a declaration form is incomplete or shows that the patent is not eligible for listing"). Yet FDA has never informed Novo that its amended use code narrative

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[10] FDA has also accepted use codes for at least two other diabetes drugs that, like Novo's amended use code, describe the approved indication of the drug: U-827 ("Use for treatment of diabetes, particularly type 2 diabetes") and U-412 ("Treatment of type 2 diabetes"). J.A. 425-26 ¶¶ 35-36. The relevant patents—Nos. 6,559,188 and 6,303,146—do not expressly claim approved combination therapies.

was "not provided in full," or that its disclosure was "incomplete." And although FDA has not appeared in this Court, the Justice Department does *not* take the position that Novo's use code narrative is incorrect in any way. *See* U.S. Br. 33.

3. Caraco maintains that Novo's use code narrative *must* be incorrect because Novo is purportedly "blocking Caraco's Section viii carved-out labeling by describing its patent in an overbroad manner." Caraco Br. 48-49. Caraco is thereby accusing Novo of committing a federal crime, but it cannot back up this outrageous accusation: Caraco does not identify *any* statute or regulation that Novo's current use code narrative transgresses, because there is none. On the contrary, Novo's use code complies with *all* applicable guidance—including FDA's *express* authorization of indication-based use codes. *See* J.A. 423-24. Indeed, a brief perusal of the Orange Book reveals dozens of such use codes, many broader than the one here, including many drafted by FDA itself. *See* U-118 ("Method of lowering blood sugar level"); U-185 ("Method of treating hypertension"); U-279 ("Method of use of the approved product"); U-305 ("Methods for using the drug product"). Caraco's position, if accepted, would require rewriting (and greatly expanding) the Orange Book.

Just as "there is nothing sinister in so arranging one's affairs as to keep taxes as low as possible (*Comm'r of Internal Revenue* v. *Newman*, 159 F.2d 848, 850-51 (2d Cir. 1947) (Hand, J., dissenting)), nor is there anything wrong with Novo's election to frame its use code in a manner that complies with all applicable statutory and regulatory guidance while channeling infringement disputes into pre-approval Paragraph IV litigation rather than post-approval litigation after the generic drug goes to market with a section viii carve-out label. *See* Pet. App. 21a (Clevenger, J., concurring). Given the choice be-

tween a use code narrative tied to the indication or one tied to the method of use—a choice expressly permitted by FDA—Novo was under no obligation to adopt the use code that would most benefit Caraco. Complying with a regulatory regime is not "gam[ing]" it, as Caraco insinuates. Caraco Br. 45.

Caraco's misguided insistence that use code narratives must "describe the patent's scope" (Caraco Br. 50) is just a collateral attack on FDA's longstanding decision to permit a drug's approved indication to serve as a use code—and, more particularly, its decision to accept Novo's use code narrative over Caraco's objection. The proper forum for such an attack is not a counterclaim against Novo but instead a lawsuit against FDA under the APA. *See Andrx Pharms., Inc.* v. *Biovail Corp.*, 276 F.3d 1368, 1378-79 (Fed. Cir. 2002) ("the APA provides an appropriate mechanism for reviewing the lawfulness of the FDA's action"). That is entirely consistent with the background rule that submissions to FDA may *not* be challenged in private litigation. *See Buckman*, 531 U.S. at 353. Indeed, Caraco conceded at the petition stage that it could have challenged FDA's refusal to authorize its section viii carve-out but failed to do so. *See* Pet. 20. Yet neither Caraco nor its *amici*, including the government, even *acknowledge* the APA in their merits submissions to this Court.

At almost every turn, Caraco challenges FDA's decisions—to allow NDA holders to propose use code narratives, to allow use code narratives based on methods *or* indications, to allow only limited challenges to use code narratives, to base section viii determinations on use code narratives. *See* 68 Fed. Reg. at 36,682-83. The counterclaim should not be distorted to allow such collateral attacks on agency decisions in the context of private litigation to which FDA is not even a party. Rather, Caraco (or any other allegedly aggrieved party) must proceed directly

against FDA, in an appropriate forum, under the APA.[11]

B. Enjoining Novo Would Be Inequitable

Caraco asks this Court to "reinstate" the district court's injunction (Caraco Br. 47), but that court did not require Caraco to demonstrate (1) "that it has suffered an irreparable injury"; (2) "that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted"; (3) "that remedies available at law, such as monetary damages, are inadequate to compensate for that injury"; and (4) "that the public interest would not be disserved by a permanent injunction." *eBay*, 547 U.S. at 391. These prerequisites to equitable relief each point in a single direction here: Caraco is not "entitled" to an injunction.

1. Caraco cannot establish any irreparable injury that would occur in the absence of an injunction, for the simple reason that Caraco's goods have been seized for failure to comply with safe manufacturing practices, and Caraco is enjoined from making additional drug products until FDA is satisfied that it has fixed these problems. J.A. 642-73. Even if Caraco were permitted to pursue a section viii statement,

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[11] The Obama Administration's support for Caraco's position, albeit lukewarm, is perplexing because most if not all of the concerns raised could be addressed by FDA, prospectively, through notice-and-comment rulemaking. *See* U.S. Cert. Br. 17-18; *see also PLIVA, Inc.* v. *Mensing*, 131 S. Ct. 2567, 2582 (2011) ("Congress and the FDA retain the authority to change the law and regulations if they so desire"). That FDA has not done so indicates that the concerns raised by Caraco and its *amici* are either illusory or countermanded by competing considerations.

and even if it were to obtain FDA approval to market generic repaglinide, it could not go to market. And that alone is sufficient to preclude the injunctive relief sought by Caraco.

2. At the same time, requiring Novo to change its use code narrative would cause irreparable harm. As noted above, FDA has permitted use code narratives based on either the approved indication or the method of use. The counterclaim provision gives Caraco no license to enlist a federal judicial officer to force Novo to choose between these two equally permissible alternatives. Indeed, if the statute were so construed it would give rise to serious constitutional problems. *See Hurley* v. *Irish-Am. Gay, Lesbian & Bisexual Group*, 515 U.S. 557, 579 (1995). "[W]here an otherwise acceptable construction of a statute would raise serious constitutional problems, the Court will construe the statute to avoid such problems." *Edward J. DeBartolo Corp.* v. *Fla. Gulf Coast Bldg. & Constr. Trades Council*, 485 U.S. 568, 575 (1988); *see United States* v. *X-Citement Video, Inc.*, 513 U.S. 64, 78 (1994).

3. Caraco has several adequate alternative remedies. FDA rejected Caraco's request for a labeling carve-out based on its previous acceptance of Novo's use code and denied Caraco's administrative challenge to that use code. 21 C.F.R. § 314.53(f). While Caraco complains about the robustness of FDA's review procedures, all agencies must make decisions on how to allocate their resources and expertise. Yet again, Caraco is really complaining about FDA—a non-party—rather than Novo. But Caraco never sought judicial review of FDA's denial of administrative relief under the APA, even though the conceded *availability* of such review establishes another alternative remedy that could have vindicated the interests Caraco now seeks to assert. It similarly puts to

rest any argument that judicial review under the counterclaim is "necessary." Caraco Br. 38.

4. Finally, the public interest favors Novo. Caraco suggests that allowing its counterclaim could lower the price of prescription medication by making generic drugs more widely available. Caraco Br. 44. This is, however, only one-half of the relevant inquiry. The Hatch-Waxman Act "strike[s] a balance between two *competing* policy interests: (1) inducing pioneering research and development of new drugs and (2) enabling competitors to bring low-cost, generic copies of those drugs to market." *Caraco Pharm. Labs, Ltd.* v. *Forest Labs., Inc.*, 527 F.3d 1278, 1282 (Fed. Cir. 2008); *see also, e.g.*, *Teva Pharm. Indus. Ltd.* v. *Crawford*, 410 F.3d 51, 54 (D.C. Cir. 2005) ("Congress sought to strike a balance between incentives, on the one hand, for innovation, and on the other, for quickly getting lower-cost generic drugs to market").

Without pharmaceutical innovation, the generic manufacturers would have nothing to copy. The patent system "encourage[s] the creation and disclosure of new, useful, and nonobvious advances," in medicine as well as other areas, by providing inventors with "the exclusive right to practice the[ir] invention for a period of years." *Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 150-51 (1989). Particularly in pharmaceutical development, where the costs of research and testing are so high, strong protection of patent rights is "necessary to encourage drug companies to expend large sums of money on research years before the product can be released to the market." Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 Va. L. Rev. 1575, 1617 (2003); *cf. Verizon Commc'ns* v. *Law Offices of Curtis V. Trinko*, 540 U.S. 398, 407 (2004).

Novo, which developed at great expense an innovative method for treating diabetes that has benefited millions of patients, has complied at all times with the detailed and reticulated regulatory regime governing prescription drugs. This meticulous compliance includes its current use code narrative, which tracks the FDA-mandated indication. A judicial order requiring Novo to change that narrative, as requested by Caraco, would upset the statutory balance to the detriment of the public.

CONCLUSION

The judgment of the court of appeals should be affirmed or, alternatively, vacated and remanded with instructions to dismiss for lack of jurisdiction.

Respectfully submitted.

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ADDENDUM

Section 505 of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, codified as amended at 21 U.S.C. § 355, provides in relevant part regarding methods of use:

Section 505(b)(1) [Listing]	Section 505(b)(2) [Certification]	Section 505(c)(2) [Listing]	Section 505(j)(2)(A)(vii) [Certification]	Section 505(j)(2)(A)(viii) [Section viii]	Section 505(j)(5)(C)(ii) [Counterclaim]
The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted	[An NDA] ... shall also include-- (A) a certification ... with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval ... and (B) if with respect to the drug for which investigations ... were conducted information was filed ... for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, [the NDA shall contain] a statement that the method of use patent does not claim such a use.	If the patent information described in subsection (b) ... could not be filed ... [the NDA holder]... shall file with the Secretary the patent number and the expiration date of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted	[An ANDA] shall contain ... a certification ... with respect to each patent which claims the listed drug referred to in clause (i) or which claims a use for such listed drug for which the applicant is seeking approval ... and for which information is required to be filed under subsection (b) or (c)	[I]f with respect to the listed drug ... information was filed under subsection (b) or (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, [the ANDA shall contain] a statement that the method of use patent does not claim such a use.	If an owner of the patent or the [ANDA] holder ... for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) of this section on the ground that the patent does not claim either-- (aa) the drug for which the application was approved; or (bb) an approved method of using the drug.

Section 505 of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, codified as amended at 21 U.S.C. § 355, provides in relevant part regarding patent information:

Section 505(b)(1) [Listing]	Section 505(c)(2) [Listing]	Section 505(j)(5)(C)(ii) [Counterclaim]
(1) The applicant shall file with the [NDA] application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences.... (2) An application submitted under paragraph (1) ... shall also include-- (A) a certification ... with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (c) of this section-- (i) that such patent information has not been filed	If the patent information described in subsection (b) of this section could not be filed with the submission of an application under subsection (b) of this section because the application was filed before the patent information was required under subsection (b) of this section or a patent was issued after the application was approved under such subsection, the holder of an approved application shall file with the Secretary the patent number and the expiration date of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted.... If the holder of an approved application could not file patent information under subsection (b) of this section because it was not required at the time the application was approved, the holder shall file such information under this subsection not later than thirty days after September 24, 1984, and if the holder of an approved application could not file patent information under subsection (b) of this section because no patent had been issued when an application was filed or approved, the holder shall file such information under this subsection not later than thirty days after the date the patent involved is issued. Upon the submission of patent information under this subsection, the Secretary shall publish it.	If an owner of the patent or the [ANDA] holder ... for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) of this section on the ground that the patent does not claim either-- (aa) the drug for which the application was approved; or (bb) an approved method of using the drug.

REPLY BRIEF

No. 10-844

In the Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD. AND SUN PHARMACEUTICAL INDUSTRIES, LTD., PETITIONERS

v.

NOVO NORDISK A/S AND NOVO NORDISK, INC., RESPONDENTS

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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REPLY BRIEF FOR PETITIONERS

By Congress's design, courts may order a brand-name drug maker to "correct or delete the patent information" it "submitted under [Section 505(b) or (c)] on the ground that [its] patent does not claim * * * an approved method of using the drug." 21 U.S.C. § 355 (j)(5)(C)(ii)(I). Novo's method patent "does not claim" repaglinide administered alone, "an approved method of us[e]." Yet the "description of the patented method of use" (21 C.F.R. § 314.53(c)(2)(ii)(P)(3)) that Novo submitted "in accordance with Section 505(b) and (c)" (JA97) says otherwise. It requires correction.

Novo says the statute is but a "delisting provision" under which "an" means "any," "patent information" means "the patent number and expiration date," and "correct" is an "artifact" of "failed bills." Br. 20, 38. But to support that claim, Novo (astonishingly) substitutes the dictionary definition of "*any*" for the definition of "*an*." Compare Resp. Br. 29 with *Shorter Oxford English Dictionary* 94 (5th ed. 2002) (reprinted *infra* at 1a). And Novo ignores that "any" appears 34 times in surrounding provisions, including in a negative assertion in the very next sentence.

Congress authorized courts to "correct *or* delete" inaccurate "patent information." Yet Novo's reading admittedly leaves "correct"—the first of two available remedies—with "little or no independent work to do." Br. 38. Novo cannot say why Congress would create a counterclaim to correct typos in patent numbers. Nor can Novo explain why Congress would exchange FDA's definition of "patent information" for a definition limited to two things—dates, which cannot be reached by the counterclaim; and numbers, which brands already have incentives to state correctly.

In fact, Congress remedied not only cases where listed patents claim *no* approved use (warranting "deletion"), but cases where overbroad patent descriptions block generic marketing for *a subset* of approved uses (warranting "correction"). Novo's reading rests on the "implausible" notion that Congress handed brands "an effective extension of the patent," enabling them to block sales of concededly non-infringing products. See *Eli Lilly and Co.* v. *Medtronic, Inc.*, 496 U.S. 661, 670, 679 (1990).

ARGUMENT

I. Novo's eleventh-hour jurisdictional argument lacks merit.

Facing difficulties on the merits, Novo attempts to change the subject. This Court lacks "jurisdiction," Novo says, because Caraco "amended its ANDA" to assert a Section viii statement—as opposed to a Paragraph IV certification—as to one claim of the patent-in-suit. Br. 23. But Novo did not question jurisdiction in the Federal Circuit, and in granting certiorari without supplementing the question presented this Court "necessarily considered and rejected" Novo's position. *Stolt-Nielsen S.A.* v. *AnimalFeeds Int'l Corp.*, 130 S. Ct. 1758, 1767 n.2 (2010). And for good reason. The statutes that Novo invokes are nonjurisdictional, and in any event are satisfied.

A. Article III

Caraco meets each Article III case-or-controversy requirement—"injury in fact, causation, and redressability." *Steel Co.* v. *Citizens for a Better Env't*, 523 U.S. 83, 103 (1998). "[A] barrier that makes it more difficult" to "compete" creates an injury. *Northeastern Fla. Chapter, Assoc. Gen. Contractors* v. *Jacksonville*, 508 U.S. 656, 666 (1993). Novo's revised use

code blocks approval of Caraco's ANDA. And ordering Novo to reinstate its earlier use code will facilitate FDA approval, redressing Caraco's injury. See U.S. Invitation Br. 19.

Without addressing these core requirements, Novo says Caraco's Section viii statement "represent[ed] that there is no controversy between the parties regarding patent infringement." Br. 24. In truth, Caraco's Section viii statement stated only that there *ought not* be any controversy under Novo's *prior* use code. When Novo revised its use code, FDA rejected Caraco's Section viii statement—compelling Caraco to maintain a Paragraph IV certification "under protest" (JA724) and litigate accordingly. Cf. *MedImmune, Inc.* v. *Genentech, Inc.*, 549 U.S. 118, 130-131 (2007). Article III is satisfied.

B. Statutory jurisdiction

1. Statutory jurisdiction is provided by 28 U.S.C. § 1338(a), which grants district courts "original jurisdiction of any civil action arising under any Act of Congress relating to patents," and 28 U.S.C. § 1331, which provides jurisdiction over federal civil actions.

Ignoring these statutes, Novo says the infringement statute (35 U.S.C. § 271(e)(2)) and the counterclaim grant "jurisdiction" "only if the generic applicant maintains a Paragraph IV certification." Br. 23. But "when Congress does not rank a statutory limitation on coverage as jurisdictional, courts should treat the restriction as nonjurisdictional." *Stern* v. *Marshall*, 131 S. Ct. 2594, 2607 (2011) (quotation omitted). Novo's statutes fail this test.

Section 271, entitled "Infringement of patent," makes it "an act of infringement to submit * * * an application under section 505(j) * * * for a drug

claimed in a patent or the use of which is claimed in a patent * * * if the purpose of such submission is to obtain approval" to market the drug commercially. 35 U.S.C. § 271(e)(2). Because nothing in § 271(e)(2) "clearly state[s]" that these terms are "jurisdictional," they are not. *Arbaugh* v. *Y&H Corp.*, 546 U.S. 500, 515-516 (2006).

The same is true of § 355(j)(5)(C)(ii), which permits filing a counterclaim if a brand "brings a patent infringement action." This is a claim-processing requirement. For example, *Reed Elsevier, Inc.* v. *Muchnick*, 130 S. Ct. 1237, 1245-1247 (2010), deemed nonjurisdictional the requirement that "no civil action for infringement of the copyright in any United States work shall be instituted until preregistration or registration of the copyright claim has been made in accordance with this title." *Reed* governs here.

Because neither statute is jurisdictional, and Novo did not press this issue in the Federal Circuit, it is waived. *Stern*, 131 S. Ct. at 2608 (citing "the consequences" of "'sandbagging'").

2. Even if these statutes were jurisdictional, Novo's position would fail. *First*, the only requirement for bringing a Hatch-Waxman counterclaim is that a "patent infringement action" be pending; no Paragraph IV certification is necessary. 21 U.S.C. § 355(j)(5)(C)(ii)(I).

Novo's position thus rests on the premise that its own claim *should have been* dismissed when Caraco invoked Section viii. Even if this were correct (and it is not), jurisdiction does not turn on "events that did not occur." *Rumsfeld* v. *Padilla*, 542 U.S. 426, 448-449 (2004). Nor would dismissing Novo's claim now defeat jurisdiction. Absent contrary language in the

governing statute, "'[a]s long as a court has jurisdiction, it may hear and render a separate judgment on a counterclaim even if the opposing party's claim has been (or should have been) dismissed.'" U.S. Invitation Br. 22-23 (citation omitted).

Second, Novo errs in suggesting that infringement suits may be filed before FDA approves ANDAs "only" where there is "a Paragraph IV certification." Br. 24. To the contrary, the Act makes it "an act of infringement to submit * * * an application under section 505(j) * * * for a drug claimed in a patent or the use of which is claimed in a patent." 35 U.S.C. § 271(e)(2)(A). Certainly, ANDAs challenged under § 271(e)(2)(A) frequently include Paragraph IV certifications. But unlike other Hatch-Waxman provisions,[1] § 271(e)(2)(A) nowhere mentions Paragraph IV. Congress made the infringing act the attempt "to obtain approval" for a patented drug or use.

To be sure, Section viii should permit Caraco to carve out the patented use. But Novo's revised use code caused FDA to *reject* Caraco's Section viii statement. JA724. Novo cannot have it both ways. Having blocked FDA approval of Caraco's ANDA, Novo cannot now insist that the ANDA does not seek approval for a patented use. Indeed, in another case involving the same patent, Novo condemned the position it now takes as "perverse." *Novo Nordisk, Inc.* v. *Mylan Pharm. Inc.*, 2009 WL 7847269, *9 (D.N.J. Sept. 8, 2009) (Novo brief).

Today, Novo invokes dictum from *Eli Lilly* stating that the infringing act under § 271(e)(2) is "submit-

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[1] *E.g.*, 35 U.S.C. § 271(e)(5); 21 U.S.C. §§ 355(j)(2)(B), 355(j)(5)(B)(iii)-(iv), 355(j)(5)(D).

ting an ANDA * * * containing the fourth type of certification." 496 U.S. at 678. The Court there, however, was not addressing § 271(e)(2)'s precise scope in drug cases; it was explaining why § 271(e)(2) and (4) are inapplicable to devices.

Third, even if § 271(e)(2)(A) required a Paragraph IV certification, Caraco had one when Novo sued—and "subject-matter jurisdiction 'depends on the state of things at the time of the action brought.'" *Rockwell Int'l Corp.* v. *United States*, 549 U.S. 457, 473 (2007) (citation omitted). It is irrelevant that Caraco later invoked Section viii.

II. Novo misreads the counterclaim.

According to Novo, "the counterclaim is available only if 'the listed patent does not claim *any*' (or, equivalently, claims *no*) approved method of using the drug." Br. 29 (quoting Pet. 12a). That is, the Court must substitute "*any*" for the term Congress chose—"*an*"—because "[a] patent either 'claim[s] an approved method' of using a particular drug, or it does not." Br. 28. Accordingly, the counterclaim is merely "a delisting provision" and the remedy of "correct[ing]" inaccurate patent information a useless "artifact" of "failed bills." *Id.* at 20, 34, 38. This interpretation is textually and logically unsupportable.

A. Novo's view that "an" and "any" are interchangeable contravenes the Act's text, its context, and ordinary usage.

Novo does not deny that "any" is an "unqualified" and "sweeping" term, or that Congress used "any" 34 times in surrounding provisions—including in a *negative assertion* in the *very next sentence*. Pet. Br. 24-25. Nonetheless, invoking dictionaries and "standard grammar," Novo insists that "an" and "any" are effec-

tively interchangeable in negative formulations. Br. 29. Novo is mistaken.

1. Dictionaries and "standard grammar"

As to dictionaries, Novo cites an unspecified page of the Shorter Oxford English Dictionary as "defining 'an' with a 'preceding negative' to mean 'none at all of, no—of any kind; not even one.'" Br. 29. Initially we could not find this definition. But eventually we did—*under the entry for "any."* *Shorter Oxford English Dictionary* 94 (5th ed. 2002); see *infra* at 1a-3a (reprinting definitions). Novo thus defines the term it *wishes* appeared in the counterclaim ("any"), not the term that *does* appear ("an"). Indeed, one might say that Novo did not cite an applicable definition.

Which is not to say that Novo did not cite *any* applicable definition. Br. 29 n.5 (definitions of "an"). But Novo misconstrues its other definitions as creating a grammatical rule, when at most they show that "an" often means "any" in negative assertions. No grammatical imperative holds that "not an" necessarily "equates to 'none.'" Br. 29. That raises a question of *usage*. See *FCC* v. *AT&T Inc.*, 131 S. Ct. 1177, 1181-1182 (2011) (rejecting a so-called "'grammatical imperativ[e]'" that did "not always" hold "in ordinary usage") (citation omitted).

The definition of "*an*" in Novo's leading dictionary is quite different from its definition of "*any*," and confirms that its meaning depends upon the context:

> one, some, any, (the oneness or indefiniteness being implied rather than asserted).

Shorter Oxford English Dictionary 1 (reprinted *infra* at 2a). Here, the context confirms that "an" does not mean "any" approved use, but rather "one" or "some"

approved uses. Pet. Br. 30. The Dictionary Act points to the same result. 1 U.S.C. § 1; Pet. Br. 30 n.6.[2]

2. Usage of "an"

Nor is this an unusual use of "an." Novo mocks as "irrelevant" our examples of "an" in ordinary usage. Br. 30; see Pet. Br. 26-28. But as our examples show, "an" is commonly used in negative assertions to refer to a discrete object—be it a particular tax exemption, element of an offense, recipe ingredient, prescribed medicine, assigned text, driving direction, or judicial precedent. When a judge tells a lawyer that his brief "does not address an applicable precedent" (Pet. Br. 27), that does not ordinarily mean the lawyer failed to address *any* applicable precedent—only that he did not address a particular case.

So too with drug patents and FDA-approved uses —and one need not understand "quantum mechanics" (Resp. Br. 28) to see why. Drugs often have multiple approved uses, and related patents often claim some such uses but not others. Novo's patent claims repaglinide administered with metformin ("an approved use"), not repaglinide administered alone ("an approved use") or repaglinide administered with TZDs

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[2] Usage guides—which precisely differentiate closely related terms—typically treat "*an*" and "*any*" as separate terms, with distinct senses, having discrete entries and no cross-references. *E.g.*, Garner, *Garner's Modern American Usage* 1 (*an*), 52-53 (*any*) (3d ed. 2009); *Merriam-Webster's Concise Dictionary of English Usage* 1 (*an*), 75-76 (*any*) (2002); Morris & Morris, *Harper Dictionary of Contemporary Usage* 1 (*an*), 40 (*any*) (1975); Fowler, *A Dictionary of Modern English Usage* 1 (*an*), 31 (*any*) (2d ed. 1965); Evans & Evans, *A Dictionary of Contemporary American Usage* 3 (*an*), 36 (*any*) (1957).

("an approved use"). This does not mean that Novo's patent exists, like "Schrödinger's cat," in "multiple, inconsistent states at once." Br. 29. It means that what a patent claims must be analyzed on a use-by-use basis.

3. The counterclaim's structure

This is confirmed by the counterclaim's structure, which Novo ignores. The counterclaim requires the "*ANDA applicant*" to establish that the patent-in-suit "*does not* claim * * * an approved method of using the drug." Novo cannot explain why, that being so, courts adjudicating counterclaims should focus on what the *brand* can show its patent *does* claim. To be sure, where there is one approved use, whether a patent "does" or "does not" claim that use is one and the same inquiry. But where (as here) there are multiple approved uses, whether the patent claims an approved use is not an either/or proposition.

4. FDA Form 3542

Quoting a question from FDA Form 3542—"Does the patent * * * claim an approved method of use of the approved drug product?"—Novo says the answers ("Yes" or "No") confirm its either/or position. Br. 32. But that is a threshold question on a worksheet that becomes much more specific. The first question keeps brands from listing patents that do not belong in the Orange Book—like the counterclaim's "delete" function. But Form 3542 later states: "Each approved use claimed by the patent should be separately identified." Pet. 214a. It is this information that the counterclaim may "correct."

Our reading does not require "invert[ing]" the text or "substituting a definite article." Resp. Br. 30. Having shown that Novo's patent "does not claim

* * * *an* approved method," Caraco should prevail. Novo's insistence that "[a] patent either 'claim[s] an approved method' of using a particular drug, or it does not" (Br. 28), by contrast, presents a false choice and requires substituting "any" for "an."

5. Hatch-Waxman as a whole

By Novo's lights, the counterclaim must be "harmonized with" Hatch-Waxman's "listing provisions," but "has *nothing to do* with section viii." Br. 32, 33. Yet the counterclaim and Section viii provide remedies to *generics*, whereas the listing provisions govern *brands*. Moreover, Novo's counsel hailed the decision below as an "important decision construing the Hatch-Waxman counterclaim and section viii carve-outs"—a decision that would "benefit" brands "in the method of use context, where the FDA looks to use codes * * * in evaluating requests by ANDA applicants for section viii carve-outs." Mark A. Perry, *Federal Circuit Issues Important Decision Construing the Hatch-Waxman Counterclaim and Section viii Carve-Outs*.[3]

Our reading of the counterclaim complements both the listing provisions and Section viii. Novo's, by contrast, directly contravenes the text, which authorizes courts not only to "delete" (*delist*) patents, but to "correct" overbroad patent descriptions. That alone forecloses Novo's suggestion (at 34) that Congress intended only to address *Mylan*. Pet. Br. 31-33; U.S. Br. 30-33.

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[3] http://www.gibsondunn.com/publications/pages/FederalCircuitDecisionConstruingHatchWaxmanCounterclaim.aspx.

Novo also errs in contending that "an" must mean "any" in the counterclaim because (they say) we "admitted" below that "the indefinite article 'a' means 'any'" in the listing provisions. Br. 33. Not so. We simply recognized that patents claiming "any" use necessarily claim "a" use. C.A. Br. 38 n.2 (brands should "list a patent if it covers any approved use"). As in the counterclaim, the listing provision uses the word "any" ("any patent") just before the term "a" ("which claims a method of using such drug"), confirming that "an" (or "a") does not *mean* "any." Yet "an" is necessarily satisfied if "any" is satisfied.

Novo cannot dispute that its reading would effectively "eviscerate" Section viii. Br. 33 & n.7. Novo's amici are still more brazen, describing "carving out the approved use" and "heading to market"—as authorized by Section viii—as a "glaring 'loophole'" that promotes "premature entry of generic drugs" and "induce[s]" infringement. Allergan Amicus Br. 4, 20.

Allergan's quarrel is with Section viii itself, which expedites generic entry only where the patent "does not claim a use for which the applicant is seeking approval." 21 U.S.C. § 355(j)(2)(A)(viii). Indeed, by authorizing labels that omit patented uses, Section viii *avoids* the "active" promotion that induced infringement requires. 35 U.S.C. § 271(b). And if it did not, brands would have a remedy. *Ibid.*

Without carve-outs, however, brands whose compound patents have long expired could easily leverage method patents claiming a sliver of the market into control of the whole market—"creat[ing] an effective extension of the patent term." *Eli Lilly*, 496 U.S. at 670. Without the counterclaim, generics would have no remedy for *that*. And the notion that Congress

viewed misrepresenting patents as integral to Hatch-Waxman's "careful balance" (Allergan Br. 27) is absurd.[4]

6. Section viii

Novo also lacks a convincing response to the fact that Section viii and the counterclaim use similar language—one refers to a patent that "does not claim *a* use" approved for the branded drug, the other to a patent that "does not claim *an* approved method of us[e]."

Novo attempts to justify reading these provisions inconsistently by noting that a phrase in Section viii —"a use for which the applicant is seeking approval" —is absent in the counterclaim. Br. 31. But this phrase would be superfluous in the counterclaim, as Article III supplies the same limitation. Courts may not order "correction" of use codes where generics are *not* seeking approval for uses purportedly claimed by the patent. That would be rendering an advisory opinion. U.S. Br. 28-29 (the counterclaim applies "only when a generic manufacturer genuinely seeks to market the drug"). By contrast, Section viii governs

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[4] Amicus Allergan says Hatch-Waxman always "requires [filing] *both* a [Paragraph IV] certification *and* a section viii statement." Br. 22. Like Novo (Br. 23), however, FDA rightly disagrees. 68 Fed. Reg. 36676, 36682 (June 18, 2003). Section viii is *conditional*—it is triggered only "if" certain information is filed. Moreover, Allergan's hypothetical, where approval is sought only "for a use not claimed by the method [patent]" (Br. 22), does not call for a Paragraph IV certification, because the hypothetical patent does not claim a use "for which the [ANDA] applicant is seeking approval." 21 U.S.C. § 355(j)(2)(A)(vii).

"fil[ings] with the Secretary," where there is no case-or-controversy requirement.

Novo's reading would also result in an inexplicable anomaly. Courts could "delete" misleading patent information when brands' patents claim *no* approved use, but not "correct" misleading patent descriptions that block marketing for *a subset of* approved uses. Yet "[a] misleading use code can cause the same practical harm (unjustified delay in a generic drug's entry into the market) as does the listing of a patent that claims *no* approved uses." U.S. Invitation Br. 16.

Even if Congress's "draftsmanship" was less than "elegant," Novo's reading—which enables brands to block generic marketing for concededly non-infringing uses—reflects an "implausible substantive intent." *Eli Lilly*, 496 U.S. at 679. Congress's "silence" in including an unnecessary phrase from Section viii cannot justify an interpretation that "is contrary to all other textual and contextual evidence." *Burns* v. *United States*, 501 U.S. 129, 136 (1991); see also *Field* v. *Mans*, 516 U.S. 59, 75 (1995) (reasoning from a negative pregnant cannot justify "results strangely at odds with other textual pointers").

7. The meaning of "correct"

Citing an *earlier* Congress's decision not to pass a bill specifying what information a counterclaimant might "correct," Novo dismisses "correct" as an "artifact" of "failed bills." Br. 38. But while this Court's "preference for avoiding surplusage constructions is not absolute" (*ibid.*), it would be strange indeed for Congress to leave such "surplusage" in the first of two verbs defining a finely tuned statute's remedies. Cf. *Chickasaw Nation* v. *United States*, 534 U.S. 84, 94 (2001) (treating a "numerical cross-reference" in "a

parenthetical" as surplusage); *Lamie* v. *United States Trustee*, 540 U.S. 526, 536 (2004) (treating one item in a list as surplusage where "the text is plain"); see *Flemming* v. *Fla. Citrus Exch.*, 358 U.S. 153, 166 (1958) (endeavoring "neither to delete nor to distort" FDCA's terms).

Moreover, where this Court has considered congressional rejection of statutory language, the Senate and House were typically considering the same bill in "tandem" during the same Congress. *E.g.*, *Hamdan* v. *Rumsfeld*, 548 U.S. 557, 579 (2006); *Lindh* v. *Murphy*, 521 U.S. 320, 329 (1997). Here, the first bill died in an earlier Congress, and FDA promulgated major reforms in the interim.

Novo is left suggesting that Congress authorized "correcting" patent information so generics could help brands fix their scrivener's errors. Novo admits that "'correc[t]' has little or no independent work to do under [this reading]." Br. 38. The only situation where Novo can imagine "correct" doing "independent work" is if a brand listed "the wrong patent number." *Ibid.*

Setting aside the implausibility of Congress passing a counterclaim to correct typos, brands already have ample incentives and opportunity to file correct patent numbers. Pet. Br. 33 & n.7.[5] If they do not, generics can file Paragraph IV certifications asserting non-infringement of the mistakenly listed patent, and brands can be denied their automatic 30-month stay of generic approval. 21 U.S.C. § 355(j)(2)(A)(vii)(IV). Further, mistakenly listed patents must be "deleted."

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[5] 21 C.F.R. § 314.53(f) permits notifying FDA of inaccurate patent information.

Novo suggests (Br. 12) but never explains how an erroneous "expiration date" can be corrected. It cannot. Under Novo's interpretation, the counterclaim is unavailable if the patent claims "*any*" approved use—regardless of an erroneous expiry. Thus, the counterclaim could never "correct" an "expiration date." Only patent numbers could arguably be "corrected," and that use of the statute is trivial. U.S. Br. 23 n.3.

B. The Act's text and regulatory context foreclose Novo's reading of "patent information."

Novo's crabbed reading of "patent information" is equally unconvincing. Novo cannot dispute that a use code "[describes] the patented method of use" (21 C.F.R. § 314.53(c)(2)(ii)(P)(3)), and thus is "information" about the "patent." And, as noted, in *no* circumstance would Novo's reading allow courts to order correction of a patent's "expiration date"—one of only two pieces of "patent information" that Novo says the counterclaim reaches.

Novo also lacks a good answer to our showing that the statute references all "patent information *submitted under*" Sections 505(b) or (c), not just "patent numbers and expiration dates." Novo would have the Court read the statute in a vacuum, ignoring closely related FDA regulations addressing the same topic—the "Submission of patent information." 21 C.F.R. § 314.53. But FDA expressly invoked Sections 505(b) and (c) as authority for those regulations. Pet. Br. 36. Moreover, unlike other Hatch-Waxman provisions, the counterclaim does not reference patent information "described in," "required under," or "prescribed by" those subsections. Pet. Br. 34 & n.8. Novo's contrary arguments are unpersuasive.

1. According to Novo, to read the phrase "submitted under subsection (b) or (c)" to include "patent information submitted under FDA regulations" is "to rewrite the statute." Br. 40. But Novo cannot explain how one "submits" patent information "under" the Act *without* submitting it under FDA regulations.

True, Congress might have cited "regulations" by "chapter and verse." Br. 43. But doing so is unusual, and certainly not required. Hatch-Waxman language referencing the "submission of information *under* a Federal law" most naturally refers to submitting such information "in furtherance of or compliance with a comprehensive scheme of regulation." *Eli Lilly*, 496 U.S. at 666-667. Likewise, "patent information submitted under [Section 505](b) or (c)" most naturally refers to submissions in compliance with regulations implementing that provision.

2. Recognizing this difficulty, Novo says FDA's regulations do *not* implement Section 505(b) or (c). Br. 45. According to Novo, FDA invoked "21 U.S.C. § 371(a)" alone, and "*actually* said" only that "'Section 505(b) and (c) of the act describes the content of an NDA and 505(b)(2) application, including the patent submission and patent certification requirements.'" *Ibid.* (citation omitted).

This argument ignores the immediately preceding sentence of the Final Rule—the first sentence under "Legal Authority"—which states: "Our principal legal authority for the final rule is section 505 of the act, in conjunction with our general rulemaking authority in section 701(a) (21 U.S.C. § 371)." 68 Fed. Reg. at 36697-36698 (reprinted *infra* at 28a). FDA thus invoked 21 U.S.C. § 371(a), as it would for any FDCA rulemaking. But the *substantive* provision that FDA

invoked was Section 505—and especially subsections (b) and (c), which address Hatch-Waxman's "patent submission and patent certification requirements." *Ibid.* All of this is what FDA "*actually* said." Resp. Br. 43.

3. Novo ignores that Section 505's patent information submission requirements for method patents are limited to patents that "claim[] a method of using [the] drug and with respect to which a claim of patent infringement could reasonably be asserted." 21 U.S.C. § 355(b)(1)(G); Pet. Br. 37-38. Novo cannot explain how FDA would ascertain that the requisite numbers and dates were filed without knowing the claimed method of use or that the patent supports an infringement claim—which is what use codes reveal. As FDA noted, "specific information on the approved methods of use protected by a submitted patent" is "essential" to "implement[ing] the [Paragraph IV] certification and section viii statement provisions." 68 Fed. Reg. at 36682-36683.

4. Noting that "'under' * * * must draw its meaning from its context" (Br. 42 n.9), Novo dismisses this Court's explanation in *Ardestani* v. *INS* that, when followed by a statute, "under" most naturally refers to regulatory proceedings conducted "'by reason of the [statute's] authority.'" 502 U.S. 129, 135 (1991). According to Novo, "[t]he context here has nothing to do with FDA regulations." Br. 42 n.9.

Novo is blinking at reality. The statutory text—"patent information submitted under [Section 505](b) or (c)"—parallels the regulatory text—"Submission of patent information * * * under section 505(b) of the act" and "patent information submitted" and "provided in accordance with Section 505(b) and (c)." Pet.

Br. 40. It is not credible to suggest that "Congress did not even hint *in the counterclaim* that it was referring to [FDA's] regulations." Resp. Br. 43.

Indeed, this Court has relied on Congress's *silence* concerning FDA rules, when "amend[ing] the [FDCA] in *other* respects," as evidencing ratification. *United States* v. *Rutherford*, 442 U.S. 544, 554 n.10 (1979) (emphasis added). Congress was anything but silent here. After hearing extensive testimony about FDA's regulations, Congress repeatedly referenced them and authorized a counterclaim using nearly identical language. It is untenable to think Congress rejected FDA's definition of "patent information" in favor of one limited to two items submitted to FDA—half of which (dates) could not be reached by the counterclaim, and half of which (numbers) brands have every reason to state correctly.

5. Nonetheless, citing a 2002 bill that would have required brands to submit information on "the approved use covered by the [patent's] claim," Novo insists that our interpretation "'resurrect[s] [a] scheme rejected by Congress.'" Br. 44 (citation omitted). But this "drafting history" was superseded by FDA's decision to define "patent information" to include a "description of the patented method of use." 21 C.F.R. § 314.53(c)(2)(ii)(P)(3). At that point, (a different) Congress no longer needed to define "patent information" to include use codes; it could simply reference the information submitted to FDA—which is what it did, with support from both sides of the aisle. *E.g.*, 149 Cong. Rec. 16689 (2003) (Sen. Hatch).

What FDA could *not* do, however, was authorize judicial intervention if brands filed inaccurate patent information. 68 Fed. Reg. at 36683. "[L]egislation

would be needed to finish the job." 149 Cong. Rec. at 15516 (Sen. Schumer). The bill actually adopted thus "provide[d] a critical complement to the work the FDA has done in clarifying its regulations on patent listing, but it goes much further." *Legislative and Regulatory Responses to the FTC Study on Barriers to Entry in the Pharmaceutical Marketplace: Hrg. Before S. Comm. on Judiciary*, 108th Cong. 19 (June 17, 2003).

That is, Congress expressly "enforce[d] the patent listing requirements at the FDA" by allowing generics "to file a counterclaim to have the brand drug company delist the patent or correct the patent information in FDA's Orange Book." 149 Cong. Rec. at 31200. Novo's naked assertion (at 46) that Congress "agreed not to make th[e] same information" required by FDA "subject to the counterclaim" is baseless.

FDA's regulations also illustrate why Congress's Members referred to "patent information," not "use codes." Resp. Br. 36-37. FDA had just defined that term and, to that point, *itself* wrote use codes. *Id.* at 37. But once use codes were written by *brands*, Congress needed a mechanism for judicial "correction." See U.S. Br. 10.

6. Novo also suggests that, if everything brands submitted to FDA were "patent information," then FDA would have to publish it under § 355(c)(2), yet FDA does not do so. Br. 41-42. But unlike Novo's example of information that is not published—"e-mail addresses of agents" (*id.* at 42)—use codes are actually "information" about a "patent," and FDA *does* publish them. JA500-595.

In sum, had Congress desired a "far narrower" provision (Br. 44), it easily could have allowed court

orders to correct "the patent number or expiration date." Instead, acting against the backdrop of FDA regulations defining "patent information" to include brand-submitted use codes, Congress authorized courts to correct "patent information submitted under Section 505 (b) or (c)." Congress's decision must be respected.

III. Novo's patent description requires reinstating the district court's injunction.

Novo also misunderstands the counterclaim's remedial language. According to Novo, its use code is "correct," and in any event Caraco must "satisfy the traditional four-factor test for injunctive relief." Br. 46-47. Novo is twice mistaken.

A. Novo's view that patent descriptions need only track drug labels contravenes the Act and FDA's regulations.

1. Novo ignores our demonstration that the term "correct" describes not a standard for avoiding liability, but the remedy for meeting the statute's requirements. Pet. Br. 48. It follows, however, that because Novo's patent does not claim two of three approved uses of repaglinide, yet FDA rejected Caraco's request to carve out the sole patented use, Novo's use code requires correction.

We know what a proper use code looks like. Novo's first submission ("use of repaglinide in combination with metformin to lower blood glucose" (JA99)) accurately reflected the lone use claimed by Novo's patent. Novo's expanded narrative does not.

2. Novo nonetheless insists that "there is nothing to 'correct.'" Br. 46-47. Quoting a snippet from 21 C.F.R. § 314.53(c)(2)(ii)(P)(1), Novo repeatedly says

FDA lets brands describe "each approved method of use *or* indication." *E.g.*, Br. 48. But that requirement is joined to later requirements by a *conjunctive*, requiring brands to provide both "a description of each approved method of use or indication * * * and * * * the description of the patented method of use." 21 C.F.R. § 314.53(c)(2)(ii)(P)(1)-(3). The notion that use codes may be divorced from patent claims grossly misrepresents FDA's regulations. U.S. Br. 4, 23.[6]

3. Citing an earlier PRANDIN use code, Novo argues that "if this indication-based use code created by FDA was proper," then the use code here "must be proper." Br. 50. But indication-based use codes are incorrect only where (as here) they misrepresent the patented method(s) of use. And since the PRANDIN use code described *a different patent* (the '924 patent), its validity depends on *that patent's* claims.

4. Unable to satisfy FDA's regulations, Novo suggests that describing the patent's scope is the job of "the patent itself—not the use code." Br. 47. In fact, both the patent and the "patent use code" (JA500) describe the patent's scope, but for different purposes and at different levels of detail. By analogy, there are several ways of describing where one lives. To complete a real estate transaction, one needs a deed describing the property's metes and bounds; but to give friends driving directions, a street address suffices.

So too with patents and patent use codes. To review patent applications, the PTO requires a "metes and bounds" description. But "[t]o effectively imple-

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[6] Contrary to Novo's assertion (Br. 51), the Solicitor General represents FDA, which lacks independent litigating authority.

ment the certification and section viii statement provisions" (68 Fed. Reg. at 36682), shorter descriptions suffice. Novo questions FDA's ability to discern method patents' claims from "a 240-character tweet." Br. 48. Yet the descriptions must be "accurate and detailed" (68 Fed. Reg. at 36682), and Novo's initial, 71-character narrative—which all agree is accurate—served its purpose with 169 characters to spare.

5. Novo denies "committing a federal crime." Br. 51. But unlike Hatch-Waxman provisions targeting "untrue," "false or misleading" statements (21 U.S.C. §§ 355(j)(4)(K), (d)(7)), the counterclaim asks whether patent information requires "correcting," given what the patent "does not claim." Pet. Br. 51. Caraco has met this burden, requiring issuance of an order.

B. *eBay*-style balancing is unauthorized, but would warrant relief.

Nor does Caraco's right to an order turn on *eBay*-style balancing. Resp. Br. 53-56. Novo waived this argument by not raising it below. *Stern*, 131 S. Ct. at 2608; Caraco C.A. Br. 59 n.4. But *eBay* applies only where courts have the option of awarding damages—which are unavailable here—and in any case the equities overwhelmingly favor Caraco.

1. *eBay* is doubly inapposite. The Patent Act authorized two remedies—damages and injunctions—and "provide[d] that injunctions 'may' issue 'in accordance with the principles of equity,'" "on such terms as the court deems reasonable." *eBay Inc.* v. *MercExchange, LLC*, 547 U.S. 388, 392 & n.2 (2006) (citation omitted).

By contrast, the counterclaim authorizes *one* remedy—"an order requiring the [brand] to correct or delete the patent information"—and states that ge-

nerics "shall not be entitled to damages." 21 U.S.C. § 355(j)(5)(C)(iii). Congress gave no indication that this remedy is discretionary, limited by "principles of equity," or subject to "terms [that] the court deems reasonable." *eBay*, 547 U.S. at 392 n.2. Courts have no "mandate" to "strike a balance of equities"; "the balance has been struck." *TVA* v. *Hill*, 437 U.S. 153, 194 (1978).

2. Even if *eBay* applied, Caraco would satisfy it. *First*, an order correcting Novo's use code would thereafter enable petitioners to sell repaglinide through Caraco, Sun, or, if necessary, "a third party." JA645-646, JA661; Pet. Supp. Br. 10-11.[7] And in all events, the order would eliminate a "sufficient cause[]" of Caraco's injury. *Khodara Envt'l, Inc.* v. *Blakey*, 376 F.3d 187, 195 (3d Cir. 2004) (Alito, J.).

Second, damages are unavailable and Caraco cannot successfully sue FDA. Resp. Br. 52. Courts have repeatedly held that "patent law" is "outside" FDA's "expertise and authority." 68 Fed. Reg. at 36683 (collecting decisions). Indeed, "the very enactment of the counterclaim provision assumed that no alternative remedy was available." Pet. 51a (Dyk, J., dissenting).

Third, the balance of harms powerfully favors Caraco, whose products concededly do not infringe. Caraco's lost market share cannot be recouped, whereas Novo cannot articulate any cognizable harm to itself in restoring its original use code—except the absurd notion that the First Amendment protects its right to submit incorrect patent information to FDA. Br. 54.

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[7] Upon request, Caraco will lodge supporting documentation with the Clerk.

Fourth, "the public interest" abhors "conduct which unfairly tends to destroy competition." *Spectrum Sports, Inc.* v. *McQuillan*, 506 U.S. 447, 458 (1993). Novo enjoyed a 17-year monopoly. It should not enjoy "an effective extension of the patent term" (*Eli Lilly*, 496 U.S. at 670) by manipulating FDA into blocking non-infringing low-cost medicines, at the expense of ill patients, let alone under an Act designed to expedite generic competition. U.S. Br. 26-33.

CONCLUSION

The judgment below should be reversed, and the district court's injunction reinstated.

Respectfully submitted.

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NOVEMBER 2011

APPENDIX

Shorter Oxford English Dictionary
(5th ed. 2002)

[Page 94]

any */ˈɛni/ adjective* (in mod. usage also classed as a *determiner*), *pronoun, & adverb.*

[Old English *ænig* = Old Frisian *ēnich*, Old Saxon *ēnig*, Middle Low German *einich*, Middle Dutch *ēnich* (Dutch *eenig*), Old High German *einag* (German *einig*), Old Norse *einigr*, Gothic *ainaha*, from Germanic: see ONE *adjective, noun & pronoun*, -Y[1].]

►A *adjective.* 1 *gen.* As *sing.*, a –, some –, no matter which, or what. As *pl.*, some—no matter which, of what kind, or how many: ▸a Used primarily in interrogative, hypothetical, and conditional contexts. OE. ▸b With a preceding negative (expressed or implied): none at all of, no—of any kind; not even one. OE. ▸c In affirmative senses: every one of (the sort named). ME.

2 With quantitative emphasis: ▸a A quantity or number of, however great, or however small. E16. ▸b A large or considerable (number, amount, etc.). *colloq.* M19.

3 With qualitative emphasis: of any kind or sort whatever; one or some, however imperfect. M19.

* * *

[Page 73]

an *adjective* (*indef. article*) see A *adjective.*

* * *

[Page 1]

a /ə; *stressed* eɪ/ *adjective* (usu. called the *indefinite article*; in mod. usage also classed as a *determiner*). Before a vowel sound (see below) **an** /ən; *stressed* an/.

[Old English *ān* one, weakened to proclitic form in early Middle English]

►**I 1** One, some, any, (the oneness, or indefiniteness, being implied rather than asserted). OE. ▸**b** One like. LME.

2 Before quantifiers: some, a matter of, about. *obsolete* exc. *dial.* & in a few, a great many, a good many. OE.

3 A certain, a particular. ME. ▸**b** A single; the same. M16.

🕮 **1** SHAKES. *Wint. T.* I have ... said many A prayer upon her grave. KEATS I had a dove and the sweet dove died. C. TOMLINSON As good a student As any in the house. M. LASKI They had passed and repassed each other a dozen times. J. BETJEMAN In Ealing on a Sunday Bell-haunted quiet falls. **b** SHAKES. *Merch. V.* A Daniel come to judgment. TENNYSON Shall I weep if a Poland fall? **2** WILLIAM TURNER Stepe them a fiue or sixe dayes in vineger. **3** *Notes & Queries* It was popularized by a Mr. Trudgen. *once upon a time.* **b** SHAKES. *Haml.* These foils have all a length? E. DICKINSON I'll tell you how the Sun rose—A ribbon at a time.

►**II 4** In, to, for, each. (Orig. the preposition *a*, Old English *an*, *on*, defining time, as in twice *a* day; afterwards identified with the indef. article, and extended from time to space, measure, weight, number: see A *preposition*[1] 3.) OE.

🕮 **4** DEFOE Four pieces of eight a man. YEATS But always went to chapel twice a week. *Oxford Times* Teams of six a side, each member of the one team fighting a duel with the six members of the other. J. STALLWORTHY Roast chestnuts, a shilling / a bag.

¶ *An* is freq. before a consonant to end of 13, before sounded *h* until 18. In standard English *an* is now used before a vowel sound (including *h* mute), as *an egg*, *an honour*; *a* before a consonant (including sounded *h* and *eu-*, *u-* pronounced /ju, ju:/) as *a pen*, *a host*, *a eunuch*, *a unit*. But before an unaccented syll., some retain *an* before sounded *h*, as *an historian*, a smaller number before *eu-*, *u-*, *as an university*.

* * *

UNITED STATES CODE

Title 35—Patents
Part III—Patents and Protection of Patent Rights
Chapter 28—Infringement of Patents

§ 271. Infringement of Patent

(a) Except as otherwise provided in this title, whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent.

(b) Whoever actively induces infringement of a patent shall be liable as an infringer.

(c) Whoever offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.

(d) No patent owner otherwise entitled to relief for infringement or contributory infringement of a patent shall be denied relief or deemed guilty of misuse or illegal extension of the patent right by reason of his having done one or more of the following: (1) derived revenue from acts which if performed by another without his consent would

constitute contributory infringement of the patent; (2) licensed or authorized another to perform acts which if performed without his consent would constitute contributory infringement of the patent; (3) sought to enforce his patent rights against infringement or contributory infringement; (4) refused to license or use any rights to the patent; or (5) conditioned the license of any rights to the patent or the sale of the patented product on the acquisition of a license to rights in another patent or purchase of a separate product, unless, in view of the circumstances, the patent owner has market power in the relevant market for the patent or patented product on which the license or sale is conditioned.

(e)(1) It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

(2) It shall be an act of infringement to submit—

(A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act

for a drug claimed in a patent or the use of which is claimed in a patent,

(B) an application under section 512 of such Act or under the Act of March 4, 1913 (21 U.S.C. 151-158) for a drug or veterinary biological product which is not primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques and which is claimed in a patent or the use of which is claimed in a patent, or

(C)(i) with respect to a patent that is identified in the list of patents described in section 351(l)(3) of the Public Health Service Act (including as provided under section 351(l)(7) of such Act), an application seeking approval of a biological product, or

(ii) if the applicant for the application fails to provide the application and information required under section 351(l)(2)(A) of such Act, an application seeking approval of a biological product for a patent that could be identified pursuant to section 351(l)(3)(A)(i) of such Act, if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug, veterinary biological product, or biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

(3) In any action for patent infringement brought under this section, no injunctive or other relief may be granted which would prohibit the making, using, offering to sell, or selling within the United States or importing into the United States of a patented invention under paragraph (1).

(4) For an act of infringement described in paragraph (2)—

(A) the court shall order the effective date of any approval of the drug or veterinary biological product involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed,

(B) injunctive relief may be granted against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug, veterinary biological product, or biological product,

(C) damages or other monetary relief may be awarded against an infringer only if there has been commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug, veterinary biological product, or biological product, and

(D) the court shall order a permanent injunction prohibiting any infringement of the patent by the biological product involved in the infringement until a date which is not

earlier than the date of the expiration of the patent that has been infringed under paragraph (2)(C), provided the patent is the subject of a final court decision, as defined in section 351(k)(6) of the Public Health Service Act, in an action for infringement of the patent under section 351(l)(6) of such Act, and the biological product has not yet been approved because of section 351(k)(7) of such Act.

The remedies prescribed by subparagraphs (A), (B), (C), and (D) are the only remedies which may be granted by a court for an act of infringement described in paragraph (2), except that a court may award attorney fees under section 285.

(5) Where a person has filed an application described in paragraph (2) that includes a certification under subsection (b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), and neither the owner of the patent that is the subject of the certification nor the holder of the approved application under subsection (b) of such section for the drug that is claimed by the patent or a use of which is claimed by the patent brought an action for infringement of such patent before the expiration of 45 days after the date on which the notice given under subsection (b)(3) or (j)(2)(B) of such section was received, the courts of the United States shall, to the extent consistent with the Constitution, have subject matter jurisdiction in any action brought by such person under section

2201 of title 28 for a declaratory judgment that such patent is invalid or not infringed.

(6)(A) Subparagraph (B) Applies, in lieu of paragraph (4), in the case of a patent—

(i) that is identified, as applicable, in the list of patents described in section 351(l)(4) of the Public Health Service Act or the lists of patents described in section 351(l)(5)(B) of such Act with respect to a biological product; and

(ii) for which an action for infringement of the patent with respect to the biological product--

(I) was brought after the expiration of the 30-day period described in subparagraph (A) or (B), as applicable, of section 351(l)(6) of such Act; or

(II) was brought before the expiration of the 30-day period described in subclause (I), but which was dismissed without prejudice or was not prosecuted to judgment in good faith.

(B) In an action for infringement of a patent described in subparagraph (A), the sole and exclusive remedy that may be granted by a court, upon a finding that the making, using, offering to sell, selling, or importation into the United States of the biological product that is the subject of the action infringed the patent, shall be a reasonable royalty.

(C) The owner of a patent that should have been included in the list described in section 351(l)(3)(A) of the Public Health Service Act, including as provided under section 351(l)(7) of such Act for a biological product, but was not timely included in such list, may not bring an action under this section for infringement of the patent with respect to the biological product.

(f)(1) Whoever without authority supplies or causes to be supplied in or from the United States all or a substantial portion of the components of a patented invention, where such components are uncombined in whole or in part, in such manner as to actively induce the combination of such components outside of the United States in a manner that would infringe the patent if such combination occurred within the United States, shall be liable as an infringer.

(2) Whoever without authority supplies or causes to be supplied in or from the United States any component of a patented invention that is especially made or especially adapted for use in the invention and not a staple article or commodity of commerce suitable for substantial noninfringing use, where such component is uncombined in whole or in part, knowing that such component is so made or adapted and intending that such component will be combined outside of the United States in a manner that would infringe the patent if such combination occurred within the United States, shall be liable as an infringer.

(g) Whoever without authority imports into the United States or offers to sell, sells, or uses within the United States a product which is made by a process patented in the United States shall be liable as an infringer, if the importation, offer to sell, sale, or use of the product occurs during the term of such process patent. In an action for infringement of a process patent, no remedy may be granted for infringement on account of the noncommercial use or retail sale of a product unless there is no adequate remedy under this title for infringement on account of the importation or other use, offer to sell, or sale of that product. A product which is made by a patented process will, for purposes of this title, not be considered to be so made after—

(1) it is materially changed by subsequent processes; or

(2) it becomes a trivial and nonessential component of another product.

(h) As used in this section, the term "whoever" includes any State, any instrumentality of a State, and any officer or employee of a State or instrumentality of a State acting in his official capacity. Any State, and any such instrumentality, officer, or employee, shall be subject to the provisions of this title in the same manner and to the same extent as any nongovernmental entity.

(i) As used in this section, an "offer for sale" or an "offer to sell" by a person other than the patentee, or any designee of the patentee, is that in which the sale will occur before the expiration of the term of the patent.

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[Page 36676]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 314

[Docket No. 02N-0417]

RIN 0910-AC48

Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

* * *

[Page 36681]

* * *

g. Method-of-Use Patents—Must the "Use" Be Approved in the Approved Drug Product? The preamble to the proposed rule mentioned that patents claiming a method of use would be able to be submitted, but did not address such patents except to confirm our position that patents may not be submitted for listing

if they claim methods of use that are not approved for the listed drug or are not the subject of a pending application.

(Comment 7) Comments disagreed as to whether the method-of-use claim in a patent submitted for listing must be a use approved in the NDA. Several comments urged us to list only those patents claiming methods of use approved in the NDA or that required clinical trials. One comment argued that listing only patents for approved uses was the only way to stop NDA holders from claiming broad uses or indications not in the approved labeling. In contrast, other comments argued that the act did not prevent NDA applicants or holders or patent owners from submitting patents for listing that claimed uses not approved by FDA. Some comments stated that patent infringement is not limited to approved uses. Other comments stated that section 505(b)(1) of the act contemplates the listing of patents claiming unapproved uses if a claim of patent infringement could reasonably be asserted, citing *Purepac Pharm. Co.* v. *Thompson*, 238 F. Supp. 2d 191 (D.D.C. 2002) (*Purepac*).

(Response) If an NDA applicant or holder or patent owner intends to submit information on a patent that claims a method of use, the patent must claim a use that is described in the NDA. If we have already approved the NDA, the patent must claim a method of use that is in the labeling of the approved NDA. This has been our position since before we issued the final patent information rule in 1994 (see 59 FR 50338, 50363-50364 (Oct. 3, 1994)). The pre-existing requirement can be found at § 314.53(b) and (c)(2).

Sections 505(b) and (c) of the act support our position that only patents claiming approved methods of

use be submitted for listing. Section 505(b)(1) of the act provides that the NDA applicant "shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug * * * ." The corresponding language in section 505(c)(2) of the act is nearly identical. Only method-of-use patents "which claim the drug for which the applicant submitted the application" must be listed. "Drug" is an ambiguous term, one which, for many years, we have consistently interpreted in the Hatch-Waxman Amendments to refer to the drug product. One court has said that:

> The meaning of the word "drug" in 21 U.S.C. § 355(b)(1) cannot be determined apart from its context. Neither the FDA nor this court disputes that the definition of drug in § 321(g) covers both drug products and active ingredients. The relevant statutory section in this case, however, modifies the word "drug" by attaching the phrase "for which the applicant submitted the application." In that context the FDA's interpretation of drug as meaning drug product is consistent with and indeed required by the statute.

(See *Pfizer, Inc.* v. *FDA*, 753 F. Supp. 171, 176 (D. Md. 1990).) All of the benefits afforded NDA holders under the Hatch-Waxman Amendments, such as the 30-month stay, derive from obtaining our approval of a particular drug product. Accordingly, only method-of-use patents that claim a use of the drug product in the pending or approved application must be submitted. Method-of-use patents for uses that the NDA holder "has not chosen to make available to the public" (id. at 177) must not be submitted for listing.

This construction of the statute is also supported by the more recent case law. Since we issued the pro-

posed rule, there have been several judicial opinions discussing method-of-use patents. In *Purepac Pharm. Co.* v. *Thompson*, 238 F. Supp. 2d 191 (D.D.C. 2002), and in the related case *TorPharm, Inc.* v. *Thompson*, Civ. No. 03-0254 (D.D.C. April 25, 2003) (appeal pending for both Purepac and TorPharm), the district court held that, where a patent did not claim a use approved in the NDA, an ANDA applicant could not be required to certify to that patent, and the agency could properly find that no ANDA applicant was entitled to 180-day exclusivity on that patent. In *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003), the Federal Circuit held that an ANDA applicant does not need to certify to a patent claiming a use not covered by the applicable NDA, and there is no cause of action against an ANDA applicant for patent infringement under 35 U.S.C. 271(e)(2)(A) for patents that claim an unapproved use. In *Allergan, Inc.* v. *Alcon Labs., Inc.*, 324 F.3d 1322 (Fed. [Page 36682] Cir. 2003), the Federal Circuit issued a per curium opinion that held that a method-of-use patent holder does not have an infringement action against an ANDA applicant when the use claimed in the patent is not FDA approved and the ANDA applicant is not seeking approval of that use. These decisions are consistent with our position that sponsors must not submit method-of-use patents that do not claim an approved use for listing in the Orange Book. They also highlight the need for an improved declaration that will clarify the claimed scope of the method-of-use patents being submitted.

We have modified the required declaration relating to method-of-use patents submitted. Although we agree, as discussed in the response to comment 11 of section II.A of this document, that each individual

claim of a patent does not need to be listed on the declaration forms for drug substance and drug product patents, we do require identification of individual claims for method-of-use patents. The declarant must describe each individual method of use for which a patent is submitted for listing, and identify the corresponding language found in the labeling of the approved NDA that corresponds to that method of use. This information will expedite our review of ANDA and 505(b)(2) applications that do not seek approval for all the approved uses. In determining whether an ANDA applicant can "carve out" the method of use, rather than certify to the listed patent, we will rely on the description of the approved use provided by the NDA holder or patent owner in the patent declaration and listed in the Orange Book.

The need for accurate and detailed information related to the approved methods of use claimed in the patent being submitted for listing is underscored by the decision in *Purepac Pharm. Co.* v. *Thompson*, 238 F. Supp. 2d 191 (D.D.C. 2002). In that case, the NDA holder submitted information on a patent claiming what was later determined to be an unapproved use of the approved drug product. This submission was accompanied by the required signed declaration from the NDA holder that the patent covered the method of use for the approved product. Accordingly, we listed the patent and the use code information submitted with the patent. Years later, well after litigation over this patent was underway, the NDA holder clarified to FDA that the patent did not, in fact, claim the use for which the NDA was approved.

This submission of inappropriate patent information led to confusion and then to litigation over an

ANDA applicant's obligation to submit either a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the act or a "section viii" statement under section 505(j)(2)(A)(viii) of the act. The section viii statement, which is also applicable to 505(b)(2) applications, permits the ANDA or 505(b)(2) applicant to avoid certifying to a patent by stating that it is not seeking approval for the use claimed in the listed patent. A section viii statement does not carry the requirement for notice to the NDA holder and patent owner, and the related opportunity for a 30-month stay.

We have implemented the section viii provisions of the act by deferring to the NDA holder's or patent owner's assertion that the method-of-use patent claims an approved use of the drug product. When the NDA holder or patent owner submits a method-of-use patent for an approved NDA, we rely upon the requirements in the regulations and the required declaration as the evidence that the patent claims an approved use. Therefore, when an ANDA applicant has sought to duplicate the labeling for which the innovator has submitted the patent, and not to specifically omit, or "carve out" labeling, we require the ANDA applicant to submit a certification to that patent. A section viii statement would not be appropriate because the ANDA applicant is seeking approval for exactly the same labeling as that in the NDA for which the patent was submitted.

Our position has been that, for an ANDA applicant to file a section viii statement, it must "carve out" from the proposed ANDA labeling, the labeling protected by the listed patent. Unless the ANDA applicant can show that it is carving out certain me-

thod-of-use labeling, a section viii statement is not a correct submission for the listed patent. In *Purepac*, the court rejected our reliance on the regulations and the general declaration as a reasonable basis for this approach to implementation. The court specifically pointed to the patent submissions in the case, and noted that the NDA holder had not complied with the requirement that NDA holders submit only those patents claiming an approved use for the drug. Although the court noted that the facts in *Purepac* were unique (the NDA holder later admitted that it made its submission "without regard" to FDA's regulations), there may be other cases in which NDA holders have submitted patents claiming unapproved uses of approved drug products.

Following the *Purepac* decision, we have two options for implementing the section viii statement provisions under sections 505(b)(2)(B) and 505(j)(2)(A)(viii) of the act that intersect with the patent submission considerations described in the proposed rule. One approach would be to permit each ANDA and 505(b)(2) applicant to make its own independent decision on whether a listed method-of-use patent claims the use for which the ANDA applicant seeks approval, and then to submit a paragraph IV certification or section viii statement as the applicant sees fit. The second approach would be to require the NDA applicant or holder to identify specifically the approved uses claimed by the method-of-use patent, with reference to the approved labeling, and declare under penalty of perjury that the patent claims an approved use. This would permit ANDA and 505(b)(2) applicants, and us, to assess whether the ANDA or 505(b)(2) applicant is seeking approval for a use the sponsor states is claimed in the listed patent, and

thus determine whether the applicant must submit a patent certification or may submit a section viii statement under section 505(b)(2)(B) or 505(j)(2)(A)(viii) of the act.

In the absence of explicit statutory language, we believe an approach that requires the NDA applicant or holder or patent owner to identify the approved methods of use protected by the patent is most consistent with the general balance adopted in Hatch-Waxman. This approach permits the NDA applicant or holder to determine which patents claim its approved drug product and then, when appropriate, to resolve disputes over infringement of those patents through patent litigation. If ANDA and 505(b)(2) applicants could always avoid the possibility of a 30-month stay by asserting in a section viii statement that certain labeling for which the applicant is seeking approval is not protected by a listed method-of-use patent—despite the NDA holder's assertion to the contrary—there would be little reason for any applicant to submit a paragraph IV certification for a method-of-use patent. This approach would essentially eliminate the certification, notice, and litigation process as to any listed method-of-use patent, producing an outcome that is inconsistent with the act.

To effectively implement the certification and section viii statement provisions set out in the statute, we must have adequate information concerning method-of-use patents. Since 1994, we have requested, but not required, that NDA applicants submit to FDA information on the approved use claimed by the patent. Since the **[Page 36683]** *Purepac* case and other instances have raised questions about what aspects of the approved drug are claimed by a listed use patent,

we believe that it is necessary that an NDA holder submit more specific information on the approved methods of use protected by a submitted patent. Only with this information can we determine what submission is required of the ANDA and 505(b)(2) applicants referencing the approved drug.

We further note that we list methods of use for approved products in the Orange Book in the section on use codes. Due to the limitations of our database system and software constraints, we are limited to using 240 total characters for the use code description in the Orange Book. Traditionally, we have created the use code description for the Orange Book from the information submitted by the NDA applicant or holder. After considering the comments, and in light of the previously described litigation, we have determined that it is more efficient and accurate to ask the NDA holder to give us the exact use code description to be published in the Orange Book. Use codes are intended to alert ANDA and 505(b)(2) applicants to the existence of a patent that claims an approved use. They are not meant to substitute for the applicant's review of the patent and the approved labeling. We understand that in some cases 240 characters may not fully describe the use as claimed in the patent. The declaration, which includes the complete description of the method-of-use claim and the corresponding language in the labeling of the approved drug, will be publicly available after NDA approval.

h. Miscellaneous Patent Listing Comments. i. Should We Create an Administrative Process to Challenge Patent Listings or to De-List Patents or to Review the Listability of Patents? The proposed rule did not propose an administrative process for challenging

patent listings or for seeking removal of a patent from the Orange Book, nor did we propose a new process to internally review the patents for listability.

(Comment 8) Several comments stated that parties, such as generic drug companies and even third parties, need a method for challenging patent listings or for de-listing patents in the Orange Book. Some comments explained that the lack of an administrative procedure for challenging patent listings either encouraged NDA applicants to submit inappropriate patent information, or did not deter the practice, to delay generic competition. A number of comments maintained that FDA has more than a ministerial role and should review patents to determine if they meet the requirements for listing. Several comments contend that we have the authority to determine the attributes of the approved drug and thus to determine the appropriate patent listings. Various administrative mechanisms were suggested through which FDA could conduct a review of patents. These suggestions ranged from hiring patent lawyers to review submitted patents to development of a full administrative hearing process.

One comment stated that patent owners need an administrative process to enforce the listing of their patents because an NDA holder might "fail" to list eligible patents.

(Response) A fundamental assumption of the Hatch-Waxman Amendments is that the courts are the appropriate mechanism for the resolution of disputes about the scope and validity of patents. The courts have the experience, expertise, and authority to address complex and important issues of patent law. This final rule supports that assumption in two

ways. First, the final rule clarifies what patents must and must not be submitted for listing. This will make it easier for NDA applicants and holders and patent owners to avoid inadvertently submitting patents that do not meet the statutory and regulatory requirements. The clarification will reduce the pressure on us to intercede in patent listing disputes and will allow the courts and parties to focus on the ultimate issue of patent invalidity or non-infringement. Second, the final rule requires NDA applicants or holders or patent owners to submit detailed information and to certify to its correctness. This should further ensure that only patents meeting the statutory requirements will be submitted for listing.

We decline to create an additional administrative process for challenging patent listings beyond that already established in § 314.53(f). We also decline to create a new process for de-listing patents or for internal FDA review of patents beyond the limited review of the patent declaration described in this final rule. Section 505(b)(1) of the act directs NDA applicants to submit certain patent information. It requires that "[u]pon approval of the application, the Secretary shall publish" the patent information (emphasis added). In section 505(j)(7)(A)(ii) and (iii) the statute mandates that we publish revisions to this information every 30 days. These short time frames do not contemplate a substantive agency review of the scope of the patent and its application to the approved drug product. Indeed, the requirement of prompt publication ("upon submission"), combined with the 30-day timeframe for updating the Orange Book, are strong evidence that Congress did not intend us to undertake anything other than a ministerial action.

In addition to the absence of any statutory basis for a substantive agency review of patents, we have long observed that we lack expertise in patent matters. An administrative process for reviewing patents, assessing patent challenges, and de-listing patents would involve patent law issues that are outside both our expertise and our authority. Although we will continue to relay questions about the accuracy of a patent submission to the NDA holder (see § 314.53(f)), our patent listing role remains ministerial. Courts have upheld our determination that our role with respect to patent listing is ministerial. (See *aai Pharma* v. *Thompson*, 296 F.3d 227, 242-43 (4th Cir. 2002), *cert. denied*, 123 S. Ct. 1582 (2003); *American Biosci., Inc.* v. *Thompson, 269 F.3d 1077, 1084 (D.C. Cir. 2001)*; *In re Buspirone Patent Litigation*, 185 F. Supp. 2d 363, 371 (S.D.N.Y. 2002); *Watson Pharm., Inc.* v. *Henney*, 194 F. Supp. 2d 442, 445-446 (D. Md. 2001); *Mylan Pharm., Inc.* v. *Thompson*, 139 F. Supp. 2d 1, 10-11 (D.D.C.), *rev'd on other grounds*, 268 F.3d 1323 (Fed. Cir. 2001).) We recognize that one court has held that parties have no private right of action to seek de-listing of patents (see *Mylan Pharmaceuticals, Inc.* v. *Thompson*, 268 F.3d 1323 (Fed. Cir. 2001)). Nevertheless, it would be inappropriate and impractical for us to create regulatory mechanisms for reviewing patent listings or permitting third parties to submit patents for listing. We lack both the resources and the expertise to resolve such matters.

Furthermore, even if we were to establish an administrative process for patent review, our decisions on these patent listing matters would inevitably lead to disputes and increased litigation against us. This litigation could question whether such an administra-

tive process was within our legal authority. Even if the courts were to decide that we may review submitted patents, there would be repeated litigation over individual patent listing decisions. Given the uncertainty of the listing status of the challenged patent during the litigation, there is no assurance that, if we reviewed submitted patents, ANDAs or 505(b)(2) applications would be approved sooner and generic drugs would enter the market any more rapidly. **[Page 36684]**

We agree that there have been a few cases in which legitimate concerns have been raised about whether specific submitted patents meet the statutory requirements for submission and listing. We believe that these concerns will be adequately and efficiently addressed by the clarification of the types of patents that must and must not be submitted and by improvements to the patent information required. We further believe that even if legally permissible, it is not necessary for us to develop a patent review mechanism. The final rule permits us to allocate our limited resources to public health activities, while leaving questions of patent law to the courts, which are better able to handle such questions. This division of responsibility is fully consistent with the process established in the Hatch-Waxman Amendments.

* * *

[Page 36697]

III. Description of the Final Rule

A. Section 314.53(b)—What Patents Must Be Submitted?

1. Which Patents Would the Final Rule Require To Be Submitted?

Section 314.53(b) describes the patents for which information must be submitted. The final rule states, in relevant part, that information must be submitted on the required declaration forms for each patent that claims the drug or a method of using the drug that is the subject of the NDA and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. The patents include patents that claim:

- The drug substance (active ingredient),
- The drug product (formulation and composition), and
- A method of use.

Those patents that claim a different polymorphic form of the drug substance that is the active ingredient described in the NDA must be submitted if the applicant has test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA. The drug product (formulation and composition) patents submitted must claim the specific drug product described in the pending or approved NDA. For patents that claim a method of use, the NDA applicant or holder must submit only those patents that claim indications or other conditions of use that are the subject of a pending or approved application. Each pending or approved method of use and related patent claim must be described.

2. What Patents Must Not Be Submitted?

Section 314.53(b), as finalized, states that information on patents claiming packaging, patents claim-

ing metabolites, and patents claiming intermediates must not be submitted. Process patents also must not be submitted. The final rule clarifies that the prohibition on submission of packaging patents does not apply to patents that claim the drug product as defined in § 314.3. If a patent claims the finished dosage form of the drug product, it must be submitted for listing.

B. Section 314.53(c)—What Does the Patent Declaration Say?

Section 314.53(c)(1) describes the general requirements for submission of patent information and the conditions for acceptance of the patent information. Section 314.53(c)(2)(i) requires a person submitting an NDA, an amendment, or a supplement, to submit an original signed declaration form as part of its submission of patent information. The appropriate declaration form must be used for submitting patent information. The information required to be submitted is described. Each form seeks specific patent information and requires a signed attestation from the NDA applicant or holder or patent owner that the information is accurate and complies with the requirements of the regulations.

Section 314.53(c)(2)(ii) requires that the NDA holder submit a declaration form with information relating to the approved NDA and additional information on use codes within 30 days of NDA approval. The information required to be submitted is described. Each form includes specific patent information and requires a signed attestation from the NDA holder or patent owner that the information is accurate and complies with the requirements of the regulations. This section also requires submission of information on patents submitted for listing after NDA

approval. This declaration form is the only declaration form that we will rely on to determine whether a patent is eligible for listing based on the patent information submitted.

C. Section 314.53(c)(3)—What Is Required to Be Filed If There Are No Relevant Patents?

The final rule modifies the statement used to describe the fact that the NDA applicant or holder believes there are no relevant patents to be submitted. The language is changed to conform to the descriptions used for drug substance (active ingredient), drug product (formulation and composition) and method of use to those used in the other regulatory provisions.

D. Sections 314.95(a) and 314.52(a)—When Are Notice and Certification Required?

The final rule modifies §§ 314.95(a) and 314.52(a) to state that, if an ANDA or 505(b)(2) application is amended to include a paragraph IV certification, notice must be provided to the NDA holder and patent owner only if the application did not already contain a paragraph IV certification or there was not a full opportunity for a 30-month stay. If an ANDA or 505(b)(2) applicant changes its paragraph IV certification before the 45-day period after notice to the NDA holder and patent owner has expired, and the NDA holder or patent owner has not initiated patent litigation, such paragraph IV certification and related notice are not considered to have satisfied the requirement of providing one notice of a paragraph IV certification and a full opportunity for a 30-month stay.

* * *

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V. Legal Authority

Our principal legal authority for the final rule is section 505 of the act, in [Page 36698] conjunction with our general rulemaking authority in section 701(a) (21 U.S.C. 371) of the act. Section 505(b) and (c) of the act describes the contents of an NDA and 505(b)(2) application, including the patent submission and patent certification requirements. Section 505(j) of the act describes the contents of an ANDA, including patent certification requirements. Sections 505(b)(2)(A) and 505(j)(2)(A)(vii) of the act, respectively, require patent certifications, while sections 505(b)(3) and 505(j)(2)(B) of the act require those applicants who have made a paragraph IV certification to provide notice to the NDA holder and patent owner.

The final rule clarifies the types of patents which NDA applicants and NDA holders must and must not submit to FDA for listing in the Orange Book. It also requires a more detailed patent declaration from NDA applicants and NDA holders or patent owners using declaration forms. The specific legal authority for each provision is set forth in the preamble discussion accompanying it.

For ANDA and 505(b)(2) applicants, the final rule reduces the number of notifications sent to patent owners and NDA holders. The specific legal authority for this action is set forth in the preamble discussion of our changed interpretation.

* * *

SUPPLEMENTAL BRIEF

RECORD AND BRIEFS

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IN THE

Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD. AND SUN PHARMACEUTICAL INDUSTRIES, LTD.,

Petitioners,

v.

NOVO NORDISK A/S AND NOVO NORDISK INC.,

Respondents.

On Petition For A Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

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RULE 29.6 STATEMENT

The disclosures in the brief in opposition remain accurate.

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SUPPLEMENTAL BRIEF FOR RESPONDENTS

Contrary to the recommendation of the Acting Solicitor General, the petition should be denied.

I. THE FEDERAL CIRCUIT CORRECTLY CONSTRUED THE HATCH-WAXMAN COUNTERCLAIM

If a patent listed in the Orange Book "does not claim ... an approved method of using the drug," the patentee may be ordered "to correct or delete the patent information submitted ... under subsection (b) or (c) of this section." 21 U.S.C. § 355(j)(5)(C)(ii). The court of appeals construed this language to mean that the counterclaim is available only if the listed patent does not claim *any* approved method of use, and to allow correction only of *statutory* patent information (*i.e.*, the patent number and expiration date). Pet. App. 11a-17a.

The government assigns three errors to the court of appeals' statutory construction. *See* U.S. Br. 11-17. It is trebly wrong.

1. To invoke the counterclaim, petitioners had to show that the '358 patent "does *not* claim ... an approved method of using [repaglinide]," yet they conceded below that the patent "*does* claim an approved method of use." C.A. Stay Opp. 13. In the face of that concession, the government's contention that petitioners "properly invoked the counterclaim" (U.S. Br. 12-13) is remarkable.

The government inverts the statutory language, arguing that a challenger can show that the patent "does not claim ... an approved method" by "identify[ing] an approved method of using the drug ... that the relevant patent does not claim." U.S. Br. 12.

This inversion, however, requires substituting a definite article for the indefinite article that Congress actually used, as the government admits. *See id.* at 13 ("the '358 patent does not claim *the use* of repaglinide as monotherapy, which is 'an approved method'") (emphasis added). But courts have no license to rewrite statutes in this fashion.

The words actually enacted by Congress mean that the counterclaim is available only if the listed patent does not claim *any* approved method of using the drug, as the court of appeals recognized. Pet. App. 12a ("When an indefinite article is preceded and qualified by a negative, standard grammar generally provides that [it] means 'any'"). That is because the construction "not ... an" equates to "none." American Heritage Dictionary of the English Language 1 (4th ed. 2006) ("not a drop to drink"); *see Barnhart* v. *Thomas*, 540 U.S. 20, 26 (2003) (adopting grammatically sensible construction).

The government *concedes* that the majority's construction is a "textually plausible interpretation[]." U.S. Br. 13. That concession alone justifies denial of the petition: In the acknowledged absence of any circuit conflict, a "textually plausible" decision in a pure statutory construction case hardly "so far depart[s]" from the accepted course of judicial proceedings as to warrant an exercise of this Court's supervisory authority. S. Ct. R. 10(a).

The government, however, maintains that the alternative construction offered by Judge Dyk, dissenting below, is also "plausible." U.S. Br. 13. But it isn't: Just like the government's inversionary reading, Judge Dyk's proposal would require substituting the definite article for the indefinite. Pet. App. 42a ("'an' refers to a particular method of using the drug, that is, *the particular approved method* listed by the

NDA holder") (emphasis added). Indeed, Judge Dyk *admitted* that his alternative would necessitate inserting a word into the statute: "[T]he statute must be construed to read .... 'an [associated] approved method of using the drug.'" *Id.* at 42a-43a (bracketed word added by Judge Dyk). Adding a term to a statute "from which it is conspicuously absent more closely resembles invent[ing] a statute rather than interpret[ing] one." *Hardt* v. *Reliance Standard Life Ins. Co.*, 130 S. Ct. 2149, 2156 (2010) (internal quotation marks omitted).

Moreover, the government makes no effort to demonstrate that Judge Dyk's reading is *more* plausible than the majority's construction. Instead, the government argues that it is "more *flexible*" and, therefore, "superior." U.S. Br. 13 (emphasis added). This Court, however, has never adopted a canon of construction favoring "flexibility" (whatever that might mean); rather, when faced with competing alternatives, the Court chooses the one that best fits the statutory text, structure, and purpose. *Bhd. of Locomotive Eng'rs* v. *Atchison, Topeka & Santa Fe R.R.*, 516 U.S. 152, 162 (1996); *cf.* U.S. Br. in *Apotex, Inc.* v. *Sebelius*, No. 10-453 (Dec. 2010) ("The court of appeals was wrong to rely on its perception of the [Hatch-Waxman] statute's 'incentive structure' to displace the statutory text"). As the government implicitly concedes, when measured against *those* metrics the majority's construction is far superior.

2. The counterclaim authorizes the correction only of "the patent information submitted ... under [21 U.S.C. §] 355(b) or (c)." The government concedes that "the only patent information that Sections 355(b) and (c) *require* to be submitted is the patent number and expiration date." U.S. Br. 14; *see Valley Drug Co.* v. *Geneva Pharm., Inc.*, 344 F.3d 1294,

1296-97 (11th Cir. 2003). The majority's conclusion that the counterclaim is limited to that information (Pet. App. 14a-17a) surely is not the kind of out-of-step decision that merits this Court's intervention.

The government maintains, however, that "*everything* FDA requires NDA holders to submit in the course of seeking and maintaining approval of an NDA" is patent information "submitted ... under" Sections 355(b) or (c). U.S. Br. 14-15 (emphasis added). But the wide variety of data about patented drugs and methods collected by FDA (*see* C.A. App. A918-921), including use code narratives, are "submitted under" FDA's regulation (21 C.F.R. § 314.53)—which may be changed after notice and comment at any time—*not* Section 355(b) or (c). The government's simplistic observation that these data constitute "'information' ... about a 'patent'" (U.S. Br. 13) ignores the statutory context, which makes the counterclaim applicable only to *specific* "patent information"—that is, information "submitted under" (and thus specified in) Section 355(b) or (c). *Cf. FCC v. AT&T, Inc.*, 131 S. Ct. 1177, 1183-84 (2011) ("two words together may assume a more particular meaning than those words in isolation").

The government tries to elide the "submitted under" clause with *Ardestani* v. *INS*, 502 U.S. 129 (1991)—the only judicial decision cited in its entire brief. U.S. Br. 14. *Ardestani*, however, recognized that "[t]he word 'under' has many dictionary definitions and must draw its meaning from its context." 502 U.S. at 135. The statute here refers to "the patent information *submitted* ... under" Section 355(b) or (c). The statute in *Ardestani* did not include the word "submitted," and adoption of the *Ardestani* formulation here (as the government suggests) would impermissibly read this word out of the statute. *See*

Astoria Fed. Sav. & Loan Ass'n v. *Solimino*, 501 U.S. 104, 112 (1991).

It is telling that the government does not agree with petitioners that FDA's information-gathering regulation was promulgated under Section 355(b) or (c), such that data submitted under the regulation are indirectly submitted under those statutory subdivisions. *See* Pet. 35. Indeed, the government expressly disavows petitioners' erroneous argument that the decision below "invalidates" any FDA regulation. U.S. Br. 15 n.2. That is because FDA's regulation is *not* an interpretation of "patent information" in Section 355(b) or (c), but rather was adopted pursuant to its general rulemaking authority. *See* BIO 27-28. The Justice Department is not shy about making administrative deference arguments where appropriate; that none appears in the instant brief is a concession that there is no deference issue in this case.

3. The government complains that the decision below "hinders the effectuation of Congress's purpose in enacting the counterclaim provision." U.S. Br. 15. Of course, "vague notions of a statute's 'basic purpose' are ... inadequate to overcome the words of its text regarding the *specific* issue under consideration." *Mertens* v. *Hewitt Assocs.*, 508 U.S. 248, 261 (1993). In any event, the government badly misrepresents the purpose of the counterclaim.

The counterclaim was a congressional response to *Mylan Pharms., Inc.* v. *Thompson*, 268 F.3d 1323 (Fed. Cir. 2001), which held that a generic competitor could not assert, in an infringement action, that a patent was improperly listed in the Orange Book because it did not claim *any* approved drug or method of use. Pet. App. 13a. As construed by the majority, the counterclaim is available to any entity that finds

itself in the same position as Mylan was in *Mylan*. The congressional "purpose" is fully "effectuated."

Without mentioning *Mylan*, the government asserts that "Congress enacted the counterclaim provision ... to combat *precisely* [the] sort of manipulation" alleged by petitioners here—*i.e.*, a patentee's submission of "an overbroad description of its method-of-use patent to FDA." U.S. Br. 11 (emphasis added). This proposition has no basis in history (or reality), since—unlike in *Mylan*—"the '358 patent was appropriately listed in the Orange Book." U.S. Br. 19. Congress never contemplated such a case when it enacted the counterclaim; the decision below cannot frustrate a nonexistent congressional "purpose."

Contrary to the government's implication (U.S. Br. 16), Senator Schumer's references to "enforc[ing] the patent listing requirements" simply refer to the *Mylan* situation in which a patent was improperly listed. *Nothing* in the legislative history so much as adverts to use code narratives, much less suggests that the counterclaim was intended to reach them. And in any event, this Court interprets statutes using the language actually enacted by Congress and signed by the President, not by isolated statements from individual legislators. *See, e.g., Barnhart* v. *Sigmon Coal Co.*, 534 U.S. 438, 457 & n.15 (2002).

The government complains that "[t]he practical effect of the court of appeals' decision ... is to preclude judicial enforcement of FDA's directive that NDA holders accurately describe their method-of-use patents." U.S. Br. 16. FDA, however, has ample authority to enforce its own "directives" and, absent express congressional authorization, the accuracy of FDA submissions may not be challenged in private litigation. 21 U.S.C. § 337(a); *see Buckman Co.* v.

Plaintiffs' Legal Comm., 531 U.S. 341, 348-51 (2001). FDA has established an administrative review mechanism to allow generic competitors to challenge use code narratives and other patent listing issues. 21 C.F.R. § 314.53(f). Petitioners availed themselves of that procedure, but were unsuccessful. *See* BIO 31-32. To the extent petitioners disagree with FDA's administration of that (or any other) aspect of the Orange Book regime, their avenue for judicial review was not the counterclaim, but an Administrative Procedure Act challenge. *See Andrx Pharms., Inc.* v. *Biovail Corp.*, 276 F.3d 1368, 1378-79 (Fed. Cir. 2002). Yet petitioners never filed an APA suit.

Finally, the government argues that "[t]he Federal Circuit's decision prevents the courts from performing their traditional function of resolving disputes about the scope of patent rights." U.S. Br. 17. But the use code narrative—limited by FDA to 240 characters—does not define patent rights; rather, it provides *notice* that a particular drug or method implicates a patent. 68 Fed. Reg. 36,676, 36,683 (June 18, 2003) ("Use codes are intended to alert ANDA ... applicants to the existence of a patent that claims an approved use. They are not meant to substitute for the applicant's review of the patent and the approved labeling."). The "scope of patent rights" is defined and conferred *by the patent itself*; the federal courts, when properly invested with jurisdiction, remain fully available to adjudicate those rights. Pet. App. 14a. And Novo did identify the specific patent claim in the appropriate location on the FDA form (C.A. App. A672) ("[Box] 4.2 Patent Claim Number(s) *(as listed in the patent)*[:] Claim 4")—a fact to which neither petitioners nor the government responds.

The government apparently thinks it would be a *good idea* to allow generic competitors to more broad-

ly challenge use code narratives. *See* Pet. App. 21a (Clevenger, J., concurring). Regardless of the correctness of that contention as a matter of policy, it is plainly insufficient as a matter of law. The decision whether or not to extend the counterclaim beyond its terms is for Congress, not this Court. *Microsoft Corp.* v. *AT&T Corp.*, 550 U.S. 437, 457 (2007).

II. THIS IS AN INAPPROPRIATE VEHICLE IN WHICH TO REVIEW THE SCOPE OF THE HATCH-WAXMAN COUNTERCLAIM

The government does not dispute that this is the first appellate decision to construe the Hatch-Waxman counterclaim since it was enacted in 2003. And despite implying that "billions of dollars" could be at stake (U.S. Br. 19), the government cannot identify even *one* listed patent that could give rise to a lawsuit like this one. *See* BIO 12-13. FDA receives only a very few section viii carve-out applications each year, and the government identifies none that FDA denied because of an allegedly overbroad use code. For all that we (or the government) know, this case truly is unique. *See* U.S. Br. in *SMC Corp.* v. *Norgren, Inc.*, No. 09-412 (Dec. 2009) ("This case would be a poor vehicle to address the question presented, ... because the court of appeals' decision is unique to the facts of this particular case").

Moreover, the government admits that the use code issue could "be of no continuing importance" depending on how the Federal Circuit resolves the pending appeal on the merits. U.S. Br. 21. The government traditionally takes the position that "[t]he interlocutory posture of [a] case makes it unsuitable for review." U.S. Br. in *PLIVA, Inc.* v. *Mensing*, Nos. 09-993, 09-1039 (Nov. 2010). The government offers

no reason that this interlocutory petition should be treated differently.

Nor does the government explain its indifference to the jurisdictional impediment that would likely preclude this Court from ever reaching the counterclaim itself. As the government is forced to acknowledge, petitioners do not have a "Paragraph IV" certification with respect to the patent claim at issue. *See* U.S. Br. 7 n.1. A Paragraph IV certification is a jurisdictional predicate to *both* an infringement suit *and* the Hatch-Waxman counterclaim. Although the government maintains that "nothing in the Hatch-Waxman Amendments states that the counterclaim becomes unavailable simply because post-filing events render the initial infringement suit non-justiciable" (U.S. Br. 22), petitioners have not had a Paragraph IV certification since April 2008, *before* the counterclaim was filed. Moreover, Congress included a separate clause—not mentioned by the government—which expressly precludes similar challenges "in any civil action or proceeding other than a counterclaim [to a Paragraph IV infringement action]." 21 U.S.C. § 355(j)(5)(C)(ii)(II). If the dispute is "non-justiciable," which the government allows is a possibility, then it is non-justiciable *in toto*. The counterclaim can't be carved off.

In any event, the government does not deny that the Court would have to *decide* the jurisdictional issue—which has not yet been reviewed by the Federal Circuit—before reaching the merits of the use code dispute. *Steel Co.* v. *Citizens for a Better Env't*, 523 U.S. 83, 88-89 (1998). But this Court would undoubtedly benefit from that court's views before considering the intricacies of Hatch-Waxman jurisdiction, which is at the outer limits of Article III. *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661, 678

(1990); *see also* U.S. Br. in *DBC* v. *PTO*, No. 08-1284 (June 2009) ("those questions were not addressed by the court of appeals, which is reason enough for this Court to decline to decide them in the first instance").

Finally, the government suggests, without elaboration, that it might not always be appropriate to base a use code narrative on the approved drug indication. U.S. Br. 20. The pertinent portion of FDA's regulation (not cited by the government), however, makes clear that the patentee may include "a description of each approved method of use *or indication*" (21 C.F.R. § 314.53(c)(2)(ii)(P)(1)), and FDA's form similarly instructs patentees to include "the description of the *approved indication* or method of use that you propose FDA include as the 'Use Code' in the Orange Book" (Pet. App. 213a) (emphases added). A great many use code narratives—including many written by FDA itself, which performed this function for years—are based on approved indications. *See, e.g.*, U-412 ("Treatment of type 2 diabetes"); U-978 ("Method of treating hyponatremia"); U-982 ("A method of treating osteoporosis") (C.A. App. A881; A912). These use codes, like Novo's, fully comply with all current FDA guidance, as well as Hatch-Waxman's legislative history, which similarly focused on indications. *See* H.R. Rep. No. 98-857, pt. 1, at 21 (1984).

The counterclaim, even if available, does not authorize a court to order an NDA holder to change an accurate use code narrative. *See* BIO 30-31. As Judge Clevenger pointed out, "Novo did nothing that was illegal or forbidden" and "there is nothing illegal, or even incorrect, about Novo's current use code." Pet. App. 19a, 21a. The government doesn't disagree with this assessment, arguing instead that "[t]he

Court can decide [whether the counterclaim is available] without determining whether respondents' own use code was deficient." U.S. Br. 20. But where the decision below "would be subject to affirmance on alternative grounds[,]" the government generally takes the position that "[f]urther review is especially unwarranted." U.S. Br. in *Golan* v. *Holder*, No. 10-545 (Jan. 2011). So, too, here.

In light of all the vehicular problems, it is ironic that the government should assert that "the Court can be confident of reaching the question presented." U.S. Br. 19. And it is doubly ironic when the government asserts that certiorari is warranted because "a judicial order directing respondents to 'correct' their use code would have tangible benefits for petitioners" (*ibid.*): In fact, petitioners' plants and goods have been seized by federal agents for failure to comply with safe manufacturing policies, and petitioners do not currently have FDA approval to manufacture *any* pharmaceuticals. Caraco Form 10-Q for Quarter Ended June 30, 2010, at 17.

Ignoring the usual certiorari considerations—unique circumstances, interlocutory posture, jurisdictional impediment not yet addressed by a court of appeals, alternative grounds for affirmance, and the correctness of the decision below—the government urges review to encourage "generic competition." U.S. Br. 11. While that might be politically expedient, there is no reason in substantive law or appellate procedure to rush the use code issue to early resolution, as the Acting Solicitor General proposes.

CONCLUSION

The petition for a writ of certiorari should be denied.

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June 3, 2011

SUPPLEMENTAL BRIEF

RECO-
I AN
BRIEF-

Supreme Court, U.S.
FILED
JUN - 7 2011
OFFICE OF THE CLERK

No. 10-844

In the Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD. AND SUN PHARMACEUTICAL INDUSTRIES, LTD., PETITIONERS

v.

NOVO NORDISK A/S AND NOVO NORDISK, INC., RESPONDENTS

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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RULE 29.6 STATEMENT

The disclosures in the petition remain accurate.

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SUPPLEMENTAL BRIEF FOR PETITIONERS

As the United States confirms, the Federal Circuit's splintered decision "mak[es] it easier for NDA holders to extend their periods of exclusivity by submitting inaccurate or misleading patent information," and "will likely impair the market entry of generic drugs, with consequent harm to consumers" to the tune of "billions of dollars each year." U.S. Br. 19. Further, any "administrative steps" that "FDA might be able to take" to ameliorate this problem "are likely to be inefficacious * * * if no judicial check is available to determine whether the information an NDA holder submits accurately describes the scope of its use patent's coverage." *Id.* at 17, 18. What is more, the recurring nature of the question presented is confirmed by five amicus briefs, the views of Wall Street analysts, and the out-of-court statements of respondents' own counsel. Reply to Br. in Opp. 1-2.

As explained below, nothing in respondents' supplemental brief diminishes the importance of that question. Eight pages of respondents' 12-page brief raise merits arguments that, even if correct (and they are not), would not diminish the importance of review. Many of respondents' points mischaracterize the record or the governing statute and regulations. And respondents fail to cast doubt on the United States' conclusion that "the Court can be confident of reaching the question presented." U.S. Br. 19.

The United States' recommendation is especially significant given the rarity of such recommendations: The Acting Solicitor General has supported review on the merits in just four of 25 invitation briefs filed this Term. The petition should thus be granted.

A. Respondents' supplemental brief largely rehashes merits arguments that, even if colorable, would not diminish the importance of review.

1. Respondents lead off by repeating their merits argument that a counterclaim is unavailable because the '358 patent does claim one of three FDA-approved uses of repaglinide. Resp. Supp. Br. 1. But they continue to ignore critical aspects of the counterclaim's "text, structure, and purpose." *Id.* at 3.

Most notably, the counterclaim places the burden of proof on the *generic* drug maker. Pet. 31-32; Reply to Br. in Opp. 8. That is, the counterclaim asks not whether the *brand* can show that its patent *claims* "an approved method," but whether the *generic* can point to "an approved method" that the patent "*does not* claim." And when (as here) there are two or more FDA-approved uses of a drug, whether the patent claims an approved use is not a simple either/or proposition. It follows that, as the United States puts it: "Petitioners * * * properly invoked the counterclaim provision by alleging that, contrary to the apparent implication of the amended use code that respondents submitted to FDA, the '358 patent does not claim the use of repaglinide as monotherapy, which is 'an approved method of using the drug.'" U.S. Br. 12-13.

While acknowledging that "courts have no license to rewrite statutes," respondents continue to insist that "an approved method of using the drug" really means "*any* approved method of using the drug." Resp. Supp. Br. 2. Here again, however, they ignore our showing that this changes the meaning of the statute, which uses the word "any" in the very same provision. Pet. 31-32; Reply to Br. in Opp. 7-8.

Nor have respondents reconciled their interpretation, which limits the counterclaim to authorizing injunctions that require *deletion* of improperly listed patents, with the statutory language that authorizes injunctions to "*correct or* delete" inaccurate patent information. Reply to Br. in Opp. 8-9; Pet. 32-33. That too forecloses the suggestion that respondents' reading is "textually plausible." See Resp. Supp. Br. 2; see also Pet. 32a (Dyk, J., dissenting).

Even if the counterclaim reflected "legislative imprecision" (*Eli Lilly*, 496 U.S. at 679), respondents do not explain why Congress would want courts to order "deleting" misleading patent information when brands' patents claim *no* approved use, but not "correcting" misleading patent descriptions used to block marketing for *some subset of* approved uses. As the United States explains, "submission of an overbroad or otherwise misleading use code can cause the same practical harm (unjustified delay in a generic drug's entry into the market) as does the listing of a patent that claims *no* approved uses of the relevant drug." U.S. Br. 16.

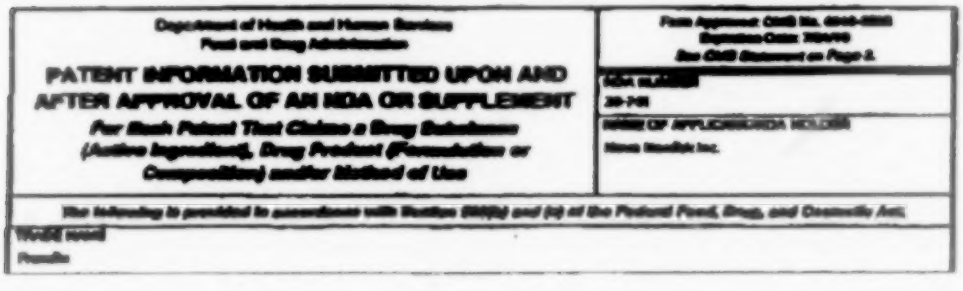
Respondents (Br. 3) deride the United States for noting that its reading of the counterclaim is "superior" to respondents' because the latter reading "directly impedes the effective implementation of the Hatch-Waxman scheme." U.S. Br. 13. But respondents concede that the statute's "purpose" is relevant to its interpretation. Resp. Supp. Br. 3. And the United States' argument is but one of many reasons why its reading is superior. Reply to Br. in Opp. 7-8.

Finally, respondents again say the counterclaim is available only "to any entity that finds itself in the same position as Mylan was in *Mylan*." Resp. Supp.

Br. 5-6. But notably absent from this argument is a citation to the actual legislative history, which nowhere cites *Mylan*. And even if "[*Mylan*] prompted the *proposal* of [the counterclaim]," "whether that alone accounted for its *enactment* is quite a different question." *Eli Lilly*, 496 U.S. at 670. As confirmed by the counterclaim's text and structure, Congress intended to do more than simply reverse that decision.

2. As the United States attests, the Federal Circuit also "gave an unduly restrictive reading to the phrase 'patent information submitted by the [NDA] holder under [21 U.S.C. 355(b) or (c)].'" U.S. Br. 12. Respondents ask the Court to accept the Federal Circuit's revision of the counterclaim to read: "information 'submitted under' (*and thus specified in*) Section 355(b) or (c)." Resp. Supp. Br. 4. But the statute does not say "specified in." It says "submitted under."

As FDA explained in 2003, "Section 505(b) and (c) of the act describes the contents of an NDA * * * application, including the patent *submission* * * * *requirements*," which are implemented by the FDA regulations entitled "*Submission of Patent Information*." 68 Fed. Reg. at 36698 (emphasis added); see also 21 C.F.R. § 314.53. Respondents thus submitted their inaccurate use code description as "patent information" on FDA Form 3542 "in accordance with Section 505(b) and (c) of the [FDCA]," just like the form says:



Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation or Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 2.

NDA NUMBER
20-741

NAME OF APPLICANT/NDA HOLDER
Novo Nordisk Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME
Prandin

Respondents say "the government does not agree with petitioners that FDA's information-gathering regulation was promulgated under Section 355(b) or (c)," and they again argue that the "*Submission of Patent Information*" regulation "was adopted pursuant to [FDA's] general rulemaking authority." Resp. Supp. Br. 5. But the United States' brief states only: "Regardless of the proper construction of the counterclaim provision, FDA's broad regulatory authority includes the power to require NDA applicants proceeding under 21 U.S.C. 355(b) and (c) to submit information relevant to drug approval." U.S. Br. 15 n.2 (citing 21 U.S.C. § 371(a)). This footnote simply recognizes that 21 U.S.C. § 371(a) grants the Secretary authority "to promulgate regulations for the efficient enforcement of [the Food, Drug, and Cosmetic Act]"; it does not (and could not) disavow FDA's statements in the Federal Register upon adoption of the "*Submission of Patent Information*" rule. And respondents do not engage our showing that FDA expressly invoked Section 505(b) and (c) as statutory authority for that regulation. Reply to Br. in Opp. 10-11.

The similarity between the term "submitted under" in the counterclaim provision and FDA's regulation entitled "Submission of Patent Information" is no coincidence. As the United States notes, "Congress was fully aware of that recent regulatory action when it enacted the counterclaim provision." U.S. Br. 14 (citing legislative history). There can be no question, therefore, that respondents "submitted" their overbroad use code description "under" FDA regulations that implement Section 505(b) and (c).

B. As the United States has confirmed, respondents' vehicular and other arguments are foreclosed by the record and otherwise lack merit.

The United States also rightly deems this case "a suitable vehicle for resolving the question presented." U.S. Br. 19.

1. Attempting to paint the case as an anomaly, respondents observe that "[t]he government does not dispute that this is the first appellate decision to construe the Hatch-Waxman counterclaim." Resp. Supp. Br. 8. But the same was true in *Eli Lilly*, in which this Court granted certiorari to address the scope of a new Hatch-Waxman defense to infringement adopted just five years prior—presumably because a definitive ruling was needed and percolation was unlikely to generate a split. See Reply to Br. in Opp. 5-6. The same factors warrant review here.

The recurring nature of the issue and the need for immediate review are confirmed by five amicus briefs—representing both industry and consumers groups—and the views of Wall Street pharmaceutical analysts. See Reply to Br. in Opp. 1-2; Pet. 23. As one commentator put it, "Wall Street * * * has signaled that, if the status quo continues, brand-name drugmakers will have found a new means of fending off unwanted generic rivals."[1] Furthermore, the United States' brief confirms that, even using "modest" assumptions, "it is reasonable to estimate that consum-

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[1] Ed Silverman, *The Supreme Court and How to Delay Generics, Pt. 2*, available at: http://www.pharmalot.com/2011/05/the-supreme-court-how-to-delay-generics-pt-2/.

ers save billions of dollars each year from approval of ANDAs with section viii statements." U.S. Br. 8.

In the end, however, one need look no further than the statements of respondents' own counsel to confirm that this is an "important" and "groundbreaking case" that, if not reversed, promises to "benefit innovator drug companies facing Hatch-Waxman counterclaims"—"especially * * * in the method of use context, where the FDA looks to use codes provided by NDA holders * * * in evaluating requests by ANDA applicants for section viii carve-outs."[2] Review is warranted to prevent this result.

2. Citing an out-of-context snippet from the United States' brief, respondents make the remarkable assertion that "the use code issue could 'be of no continuing importance' depending on how the Federal Circuit resolves the pending appeal on the merits." Resp. Supp. Br. 8 (quoting U.S. Br. 21). But as the United States notes in the following sentence: "The parties have informed us * * * that if this Court grants the petition, they will jointly move to stay proceedings in the court of appeals pending the Court's decision on the merits." U.S. Br. 21. That is indeed the parties' agreement, as confirmed by a recent motion filed by respondents.[3] The parties have thus rec-

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[2] Mark A. Perry, *Federal Circuit Issues Important Decision Construing the Hatch-Waxman Counterclaim and Section viii Carve-Outs*, available at: http://www.gibsondunn.com/publications/pages/FederalCircuitDecisionConstruingHatchWaxmanCounterclaim.aspx.

[3] See Unopposed Motion for Additional Extension of Time to File Principal Brief for Appellants Novo Nordisk A/S and Novo Nordisk Inc., Dkt. 25, No. 2011-1223 (Fed. Cir. Apr. 26, 2011).

ognized that this Court's disposition of the question presented could be case-dispositive. It is troubling that respondents would suggest that a Federal Circuit ruling could moot this case without acknowledging the parties' agreement to seek a stay of that decision if certiorari is granted. But regardless, the United States is correct that "[t]he case is not moot and is not likely to become moot." U.S. Br. 21.

3. Respondents continue to press a jurisdictional challenge to their own lawsuit—the frivolity of which is evidenced by their extended delay in raising it. See Reply to Br. in Opp. 3-4. As the United States notes, this argument "lacks merit": "the district court had federal-question jurisdiction under 28 U.S.C. 1331 or patent-law jurisdiction under 28 U.S.C. 1338. And the Federal Circuit had appellate jurisdiction because the district court's jurisdiction over respondents' original infringement suit was based on 28 U.S.C. 1338." U.S. Br. 21, 22.

Respondents cite no authority to support their view that a Paragraph IV certification is necessary to jurisdiction. They have taken the opposite view in other cases (Reply to Br. in Opp. 4-5), and have yet to explain their about-face. But in any case, respondents' jurisdictional challenge not only fails as a matter of law; it rests on mischaracterizations of both the United States' position and the record.

Respondents assert: "As the government is forced to acknowledge, petitioners do not have a 'Paragraph IV certification with respect to the patent claim at issue.'" Resp. Supp. Br. 9 (quoting U.S. Br. 7 n.1). But the government acknowledged no such thing. It stated that "FDA will not publicly confirm or deny" the status of petitioners' patent certification. U.S. Br

n.1. In fact, as the district court found, Caraco's ANDA has contained a Paragraph IV certification throughout this lawsuit. Opp. App. 10a. Respondents' statement (at 9) that "petitioners have not had a Paragraph IV certification since April 2008, before the counterclaim was filed," is false. Indeed, respondents have never denied that Caraco maintained a Paragraph IV certification as to at least one asserted patent claim (claim 5) until October 2009—*after* Caraco filed its counterclaim in June 2009 and *after* the use code injunction that forms the basis of this appeal. And even if jurisdiction over the underlying suit had lapsed, jurisdiction over the counterclaim would remain.

In sum, even if a Paragraph IV certification as to an asserted claim were a jurisdictional prerequisite for Caraco's counterclaim (and it is not), that prerequisite would be satisfied here. And the United States is right to declare with confidence: "All agree that the district court had jurisdiction over respondents' infringement action when it was filed, and that the infringement action was pending when petitioner filed the counterclaim." U.S. Br. 22.[4]

4. Respondents also misrepresent the governing regulations. Contrary to their assertion, FDA's rules do not authorize what respondents provided here—a use code description that tracks the labeled indication but is divorced from the patent's claims. Ironically, respondents criticize the United States for not quoting "the pertinent portion of FDA's regulation [21

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[4] A full summary of the facts supporting jurisdiction is available at: U.S. D. Ct. No. 2:05-cv-40188-AC-DAS, Dkt. No. 505 (statement of undisputed facts concerning subject matter jurisdiction).

C.F.R. § 314.53(c)(2)(ii)(P)(1)]." Resp. Supp. Br. 10. But it is respondents who fail to quote the relevant portion of the rule, which requires providing a "description of the patented method of use":

> (P) Information on each method-of-use patent including the following:
>
> (1) Whether the patent claims one or more approved methods of using the approved drug product and a description of each approved method of use or indication and related patent claim of the patent being submitted;
>
> (2) Identification of the specific section of the approved labeling for the drug product that corresponds to the method of use claimed by the patent submitted; *and*
>
> (3) *The description of the patented method of use* as required for publication.

21 C.F.R. § 314.53(c)(2)(ii)(P) (emphasis added). The United States' submission is consistent with these regulations (U.S. Br. 20); respondents' brief is not.

5. Finally, respondents cannot seriously challenge the United States' conclusion that "a judicial order directing respondents to 'correct' their use code would have tangible benefits for petitioners." U.S. Br. 19. Respondents state that petitioner Caraco is not currently able to manufacture repaglinide from its facility. But they cannot dispute that an order correcting respondents' overbroad use code (thus ending this litigation) would have enormous tangible benefits for petitioners Caraco and Sun. Petitioners enjoy "first applicant" status, entitling them to 180 days of generic marketing exclusivity upon FDA approval. If review is granted and the ruling below reversed, peti-

tioners will thereafter have the option to market repaglinide through Caraco, Sun, or, if necessary, a third party—long before respondents' method patent expires in 2018. Yet respondents' misrepresentation of their patent's scope has caused petitioners to have to litigate infringement for years, when the patent covering the repaglinide compound expired in 2009. This Court's intervention is needed to eliminate such delay in both this case and others.

CONCLUSION

The United States' brief confirms both the importance of the question presented and the suitability of this case as a vehicle to resolve it. Moreover, respondents' arguments on the merits do not diminish the importance of the issues or the need for immediate review. The petition should therefore be granted.

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JUNE 2011

AMICUS CURIAE BRIEF

No. 10-844

In the Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD., ET AL., PETITIONERS

v.

NOVO NORDISK A/S, ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE SUPPORTING PETITIONERS

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QUESTION PRESENTED

By filing an abbreviated new drug application (ANDA), a manufacturer may seek approval from the Food and Drug Administration (FDA) to market a generic version of a previously approved brand-name drug. The ANDA must address, *inter alia*, each patent that claims a method of using the drug. If the ANDA seeks approval for a use claimed by a patent, it must include a certification that the patent has expired, will expire, is invalid, or would not be infringed by the sale or use of the generic drug. Alternatively, the ANDA applicant may inform FDA that it seeks approval for a method of use that the patent does not claim. To determine whether an ANDA seeks approval for a patented use—and hence whether it includes the required certifications—FDA relies on information describing the relevant patent's scope submitted by the brand-name manufacturer under FDA regulations.

The brand-name manufacturer may sue the ANDA applicant for patent infringement if, *inter alia*, the ANDA seeks approval for a patented use before the relevant patent has expired. The ANDA applicant may respond with "a counterclaim seeking an order requiring the [brand-name manufacturer] to correct or delete the patent information [it previously] submitted * * * on the ground that the patent does not claim either—(aa) the drug for which the application was approved; or (bb) an approved method of using the drug." 21 U.S.C. 355(j)(5)(C)(ii)(I). The question presented is as follows:

Whether an ANDA applicant may assert a counterclaim under Section 355(j)(5)(C)(ii)(I) by alleging that the brand-name manufacturer's patent information does not accurately and precisely describe the method of use claimed by its patent.

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In the Supreme Court of the United States

No. 10-844

CARACO PHARMACEUTICAL LABORATORIES, LTD., ET AL., PETITIONERS

v.

NOVO NORDISK A/S, ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE SUPPORTING PETITIONERS

INTEREST OF THE UNITED STATES

This case presents the question whether an applicant seeking approval from the Food and Drug Administration (FDA) to manufacture a generic equivalent of a brand-name drug can challenge the accuracy and precision of certain patent information that is submitted to FDA by the brand-name manufacturer. Because patent information submitted by the brand-name manufacturer is integral to FDA's decision whether to approve generic drugs, but FDA lacks the resources and expertise necessary to determine whether that information is accurate and precise, the United States has an interest in an effective judicial mechanism for resolving such challenges. If left uncorrected, inaccurate or imprecise brand-name

patent information can delay FDA's approval of generic drugs, thereby depriving consumers of the benefits of competition between generic and brand-name manufacturers. At the Court's invitation, the United States filed a brief as amicus curiae at the petition stage of this case.

STATEMENT

1. a. Under the Federal Food, Drug, and Cosmetic Act, as amended, 21 U.S.C. 301 *et seq.*, FDA regulates the manufacture, sale, and labeling of prescription drugs. To obtain FDA's approval to market a new drug, a manufacturer must submit a new drug application (NDA). 21 U.S.C. 355(b). The NDA must contain, *inter alia*, a statement of the drug's components, proposed labeling that describes the uses for which the new drug may be marketed, and scientific data and other information demonstrating that the drug is safe and effective as labeled. 21 U.S.C. 355(b)(1). A drug approved under the NDA process is often referred to as a "brand-name" drug.

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, known as the Hatch-Waxman Amendments. To facilitate the entry of generic competitors, the Hatch-Waxman Amendments provide that, after a brand-name drug's NDA has been approved, and subject to certain periods of NDA exclusivity (see 21 U.S.C. 355(j)(5)(F)), any manufacturer may seek approval to market a generic version by filing an abbreviated new drug application (ANDA) with FDA. See 21 U.S.C. 355(j). The ANDA process does not require the generic manufacturer to provide independent clinical evidence of safety or efficacy. Instead, the ANDA must generally show, *inter alia*, that the generic drug has the

same active ingredient(s) as, and is bioequivalent to, a reference listed drug (RLD), *i.e.*, the brand-name drug to which the proposed generic will be compared. 21 U.S.C. 355(j)(2)(A)(ii) and (iv).

b. An ANDA must also explain how the generic drug can be marketed without infringing certain of the NDA holder's patents. See 21 U.S.C. 355(j)(2)(A)(vii)-(viii). To facilitate that process, NDA holders submit patent information to FDA, and FDA publishes certain information in *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the "Orange Book." See 21 U.S.C. 355(b)(1), (c)(2) and (j)(7). The patent information published in the Orange Book then serves as a frame of reference for the ANDA.

i. The Hatch-Waxman Amendments require an NDA applicant to submit "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. 355(b)(1). FDA "publish[es] in the [Orange Book] the patent number and expiration date of each patent that is required to be, and is, submitted to FDA by an applicant." 21 C.F.R. 314.53(e). FDA's implementing regulations require the applicant to submit certain additional patent information during the NDA approval process. See 21 C.F.R. 314.53. The current regulations trace to a significant 2003 rulemaking, which is discussed in detail below, pp. 7-10, *infra*.

The informational requirements applicable to method-of-use patents are of particular relevance here. Once a new drug is approved, the manufacturer must

submit "a description of each approved method of use or indication and related patent claim of the patent being submitted"; identify "the specific section of the approved labeling for the drug product that corresponds to the method of use claimed by the patent submitted"; and provide a "description of the patented method of use as required for publication" in the Orange Book. 21 C.F.R. 314.53(c)(2)(ii)(P). "[F]or each use patent," FDA publishes "the approved indications or other conditions of use covered by a patent" (commonly called a "use code"). 21 C.F.R. 314.53(e).

ii. An ANDA must account for each patent listed in the Orange Book as associated with the RLD. That requirement is easily satisfied when the listed patent has expired or the ANDA applicant is willing to await approval until the patent expires. See 21 U.S.C. 355(j)(2)(A)(vii)(II)-(III). Otherwise, the ANDA applicant has two choices with respect to a patent claiming a method of using the drug.

In appropriate circumstances, the ANDA applicant may assert that, although the listed patent claims a method of using the RLD, the ANDA applicant does not seek approval of its drug for that use. 21 U.S.C. 355(j)(2)(A)(viii). This assertion is known as a "section viii statement." If an ANDA applicant makes a section viii statement, and the ANDA is otherwise approvable, FDA may approve the ANDA without requiring any further steps relating to the patent. In that circumstance, FDA will approve appropriate labeling for the generic drug that "carves out" information related to the patented use (as described in the use code) from the RLD's existing approved labeling, thus approving the generic drug only for unpatented uses. See 21 C.F.R. 314.94(a)(8)(iv), 314.127(a)(7). Approval with carve-out

labeling is permitted, however, only if the drug so labeled will remain safe and effective for the remaining non-patented methods of use. See *ibid.* FDA will not approve an ANDA with a section viii statement if there is any overlap between the methods of using the drug reflected in (1) the carved-out labeling proposed in the ANDA and (2) the use code in the Orange Book. See 68 Fed. Reg. 36,682-36,683 (2003). In performing that comparison, FDA does not independently assess the patent's scope, but instead relies on the NDA holder's description (*i.e.*, the use code) of the method(s) of use that its patent covers.

Alternatively, if a section viii statement is not feasible (because the patent's use code effectively precludes carve-out labeling) or undesirable (because the ANDA applicant wishes to market its drug before expiration of the patent without carving out the protected use), the ANDA applicant may certify that the patent "is invalid or will not be infringed by the manufacture, use, or sale of the [ANDA applicant's] drug," 21 U.S.C. 355(j)(2)(A)(vii)(IV). This is known as a "paragraph IV certification." A paragraph IV certification cannot be premised on proposed carve-out labeling. Rather, the ANDA applicant must certify that the NDA holder's patent is invalid or will not be infringed even if the generic drug is labeled in the same manner as the RLD.

Rather than embroiling FDA in controversies over patent validity and infringement, Congress channeled disputes about paragraph IV certifications to the courts. Thus, an ANDA applicant that makes a paragraph IV certification must provide notice to the NDA holder, 21 U.S.C. 355(j)(2)(B), which may then file a patent-infringement suit in district court without waiting for some other potentially infringing act, see 35 U.S.C.

271(e)(2)(A). If the NDA holder sues within 45 days after receiving statutory notice, FDA generally may not approve the ANDA until the court finds the patent invalid or not infringed, or 30 months elapse from the NDA holder's receipt of statutory notice. See 21 U.S.C. 355(j)(5)(B)(iii). If the patent owner does not sue within 45 days, FDA may approve the application immediately, *ibid.*, though without prejudice to infringement claims the patent owner might assert when the ANDA applicant produces or markets the generic drug.

c. The Hatch-Waxman Amendments include additional provisions that further affect the length of time a brand-name manufacturer can market its drug free from generic competition. Because a brand-name manufacturer generally cannot exploit its patent until its drug is approved, the sometimes-lengthy NDA process effectively shortens the period during which the manufacturer enjoys patent protection. To address that issue, the Hatch-Waxman Amendments authorize the extension of patents on approved drugs to account for the period during which the NDA was under review at FDA. 35 U.S.C. 156(a). On the other hand, the Hatch-Waxman Amendments authorize would-be generic competitors to engage in specified preparatory activities that would otherwise constitute patent infringement, 35 U.S.C. 271(e)(1), so that generic competitors can be ready and able to market their drugs as soon as the brand-name manufacturer's patents expire. See *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661, 671-672 (1990) (discussing these changes).

2. a. The Hatch-Waxman Amendments have benefitted consumers by fostering substantial competition from generic drugs. When multiple generic competitors enter the market for a drug, the price for the drug (in

generic form) is typically 50% to 80% below the brand-name drug's price. FDA, *Generic Competition and Drug Prices*, http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm129385.htm (Mar. 1, 2010). According to Congressional Budget Office (CBO) estimates, consumers saved $8 to $10 billion in 1994 from generic drugs, and in 2007, Medicare alone (through its prescription drug benefit) saved $33 billion from generic drugs. CBO, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry* 13 (July 1998); CBO, *Effects of Using Generic Drugs on Medicare's Prescription Drug Spending* 7-8 (Sept. 2010).

Starting in the late 1990s, however, brand-name manufacturers began to exploit certain features of the original Hatch-Waxman scheme to prevent or delay FDA approval of generic competitors. See generally Fed. Trade Comm'n, *Generic Drug Entry Prior to Patent Expiration: An FTC Study* (July 2002) (*Generic Drug Entry*) (discussing manufacturers' anticompetitive behavior). In particular, some brand-name manufacturers submitted to FDA patent information that arguably was not appropriate for listing in the Orange Book. FDA was nevertheless obliged under the statute and regulations to publish that information, and the ensuing litigation prevented or delayed FDA's approval of ANDAs. See *id.* at 39-56; A-39 to A-45 (discussing Orange Book listing issues and describing several such episodes).[1]

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[1] Even if a patent cannot be listed in the Orange Book, the brand-name manufacturer may be able to assert a traditional claim of patent infringement once the generic drug is marketed. From the NDA holder's point of view, the significance of Orange Book listing is that, if the ANDA applicant makes a paragraph IV certification and the brand-name manufacturer timely commences an infringement action, FDA

In 2002, FDA initiated a rulemaking to ameliorate this situation. 67 Fed. Reg. 65,448. FDA explained that it interpreted the Hatch-Waxman Amendments to permit listing only of patents that claim the active ingredient or formulation of the approved drug, or an approved method of using the drug. FDA stated that "process patents [for making the drug], patents claiming packaging, patents claiming metabolites [*i.e.*, compounds produced in the body as a result of administering the drug], and patents claiming intermediates [*i.e.*, materials produced in processing the drug that are not present in the finished product] are not covered." *Id.* at 65,451. FDA acknowledged that its existing practice—which allowed an NDA applicant simply to declare that its patent "covers the formulation, composition and/or method of use of [the drug]"—may have proven "insufficient in practice to prevent NDA applicants * * * from attempting to list inappropriate patents." *Id.* at 65,453. FDA therefore proposed to "ask NDA applicants * * * to provide more patent information to help ensure that only appropriate patents are listed," and it "propos[ed] to require * * * NDA applicants to identify the specific pending or approved use claimed by a method of use patent." *Id.* at 65,453, 65,454.

FDA's 2003 final rule largely implemented that proposed approach. To "reduce confusion and help curb attempts to take advantage of th[e] process," FDA replaced the conclusory declarations that its prior approach had allowed with structured forms and a "rule

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approval of the ANDA is significantly delayed pending resolution of that suit. See pp. 5-6, *supra*. An Orange Book listing thus can provide the NDA holder the rough practical equivalent of an automatic preliminary injunction during the first 30 months of any infringement litigation.

[that] clarifies patent submission and listing requirements." 68 Fed. Reg. at 36,676; see *id.* at 36,707-36,712 (forms). To "ensure that only patents meeting the statutory requirements will be submitted for listing," *id.* at 36,683, the forms and rule direct the NDA holder to classify the submitted patent as claiming either a "drug substance (active ingredient)," a "drug product (composition/formulation)," or a "method of use" of the drug, *id.* at 36,711.

The forms and rule addressed method-of-use patents in further detail because mischaracterization of such patents had interfered with the agency's implementation of section viii, the provision authorizing an ANDA applicant to seek carve-out labeling to avoid a listed method-of-use patent. As FDA explained, "submission of inappropriate patent information led to confusion and then to litigation over an ANDA applicant's obligation to submit either a paragraph IV certification * * * or a 'section viii' statement." 68 Fed. Reg. at 36,682. The 2003 rule therefore "require[d] the NDA applicant * * * to identify specifically the approved uses claimed by the method-of-use patent," thereby enabling ANDA applicants and FDA to "determine whether the [ANDA] applicant must submit a patent certification or may submit a section viii statement." *Ibid.*; see *id.* at 36,685 ("The specific method-of-use claims are essential to our review [of section viii statements].").

FDA expected that the clarity and information-submission requirements of its new rule would "reduce confusion and help curb attempts to take advantage of th[e] [patent-information] process." 68 Fed. Reg. at 36,676. The agency acknowledged, however, that even its new system would ultimately depend on the accuracy of information submitted by NDA applicants. See, *e.g.*,

id. at 36,687 ("[W]e will not evaluate a patent to assess whether the declaration is accurate or whether the patent has been appropriately submitted for listing."); *id.* at 36,682 ("In determining whether an ANDA applicant can 'carve out' the method of use, * * * we will rely on the description of the approved use provided by the NDA holder or patent owner."). Although several commenters asked FDA to create an administrative process for challenging patent listings, *id.* at 36,683, FDA declined to do so. FDA explained that it "lack[s] both the resources and the expertise to resolve such matters," and that a "fundamental assumption of the Hatch-Waxman Amendments is that the courts are the appropriate mechanism for the resolution of disputes about the scope and validity of patents." *Ibid.*

b. Later in 2003, Congress complemented FDA's rulemaking by creating a judicial mechanism to resolve disputes about patent information submitted to FDA. See 149 Cong. Rec. 15,516 (2003) (statement of Sen. Schumer) ("[W]hen the FDA actually talked about closing these loopholes, it was made clear that legislation would be needed to finish the job."). Congress authorized an ANDA applicant defending a patent-infringement action to

> assert a counterclaim seeking an order requiring the [RLD NDA holder] to correct or delete the patent information submitted by the holder under [21 U.S.C. 355(b) or (c)] on the ground that the patent does not claim either—
>
> (aa) the drug for which the application was approved; or
>
> (bb) an approved method of using the drug.

21 U.S.C. 355(j)(5)(C)(ii)(I) (added by Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, § 1101(a)(2)(C), 117 Stat. 2452). Like the original Hatch-Waxman scheme for paragraph IV litigation, the counterclaim provision assigns FDA no role in deciding the scope or validity of patents, and instead channels such disputes to courts.

3. a. Petitioner Caraco wishes to market a generic version of Prandin®, respondents' brand-name version of the diabetes drug repaglinide. Respondents' patent on the repaglinide compound expired in 2009. Respondents also own a patent (the '358 patent) that will expire in 2018 and that pertains to the combination of repaglinide with another drug, metformin. Claim 4 of the '358 patent claims "[a] method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin." J.A. 96.

Petitioner submitted an ANDA seeking approval of a generic version of repaglinide upon the expiration (in 2009) of respondents' patent on the repaglinide compound. When petitioner initially filed its ANDA, respondents' use code for the '358 patent described Claim 4 as pertaining to the "[u]se of repaglinide in combination with metformin to lower blood glucose." Pet. App. 8a. Petitioner's ANDA initially included a paragraph IV certification to the '358 patent, asserting that the patent was invalid or would not be infringed by petitioner's marketing of generic repaglinide. Respondents filed a timely infringement action, thus delaying FDA's approval of petitioner's ANDA. Petitioner later amended its ANDA to replace the paragraph IV certification to Claim 4 of the '358 patent with a section viii statement, which made clear that petitioner did not seek approval

for use of the repaglinide-metformin combination therapy. FDA indicated that, once petitioner's ANDA was otherwise approvable, FDA would approve carve-out labeling that excluded the combination-therapy use (but included, for example, use of repaglinide on its own, known as "monotherapy"). *Ibid.*

Meanwhile, as part of an effort to improve the labeling of oral anti-diabetic drugs (including Prandin®), FDA asked respondents to revise Prandin®'s labeling to "[r]eplace all the separate indications [for use of the drug] (e.g., monotherapy, combination therapy, and initial or second-line therapy) with the following sentence: 'Prandin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.'" J.A. 164. Respondents complied, J.A. 31, though information about use of repaglinide in combination with metformin remained in the clinical-trials section of Prandin®'s labeling, J.A. 27. About a year later, respondents submitted to FDA an amended use code for the '358 patent that tracked the revised indication for Prandin®: "A method for improving glycemic control in adults with type 2 diabetes mellitus." Pet. App. 9a. FDA neither requested nor required that change.

Petitioner could not carve out the single approved indication that corresponded to respondents' new use code because that would leave petitioner's labeling without any approved indication, rendering its drug not safe and effective. Accordingly, FDA reversed course and disallowed a labeling carve-out. Petitioner then filed a counterclaim against respondents in the pending infringement suit, seeking an order directing respondents to revert to the old use code. That prior use code had made clear that the '358 patent does not claim the entirety of the single approved indication, but rather

claims only the use of repaglinide in combination with metformin to lower blood glucose.

b. The district court held that petitioner's counterclaim was proper and that respondents' new use code was overbroad. Pet. App. 65a-96a. The court explained that the counterclaim provision was designed to address the possibility that an ANDA applicant "could be seriously disadvantaged by an incorrect Use Code narrative." *Id.* at 93a. On the merits, the court agreed with petitioner that respondents' new use code misleadingly "suggests that [the '358] patent covers any method of improving glycemic control in adults with Type 2 diabetes." *Id.* at 71a. The district court accordingly enjoined respondents to "correct * * * [their] inaccurate description of the '358 patent by submitting to FDA [a use code] that * * * describes claim 4 of the '358 patent * * * as covering the 'use of repaglinide in combination with metformin to lower blood glucose.'" *Id.* at 65a-66a.

4. The court of appeals reversed. Pet. App. 1a-52a.

a. The court of appeals first discussed the counterclaim provision's reference to a patent that "does not claim * * * an approved method of using the drug." The court interpreted that language to apply only when the patent does not claim *any* approved method of using the drug. Pet. App. 11a-12a. The court therefore held that the counterclaim mechanism is unavailable if (as here) the listed patent claims at least one approved method of using the drug, even if the NDA holder's use code misleadingly suggests that the patent claims other approved methods of use as well.

The court of appeals found that conclusion to be further supported by the counterclaim provision's authorization of "an order compelling 'the holder to correct or delete *the patent information* submitted by the holder

under subsection (b) or (c).'" Pet. App. 15a (quoting 21 U.S.C. 355(j)(5)(C)(ii)(I)). The referenced provisions, 21 U.S.C. 355(b) and (c), require NDA applicants to submit only the patent number and expiration date of the relevant patents, not the more detailed information (including the use code) that is mandated by FDA regulations. Pet. App. 15a. The court of appeals inferred from that fact that the only relief available under the counterclaim provision is an order directing the NDA holder to delete or correct a patent number or expiration date, and that the provision is not concerned with errors or misrepresentations in a use code. *Id.* at 15a-16a.

b. Judge Clevenger concurred. Pet. App. 19a-21a. As relevant here, he agreed with the court's textual analysis, though he was skeptical that paragraph IV litigation would resolve the parties' dispute over respondents' use code. *Id.* at 19a.

c. Judge Dyk dissented. Pet. App. 22a-52a. He would have read the phrase "the patent does not claim * * * an approved method of using the drug" to encompass the situation in which information in the Orange Book incorrectly asserts that the patent claims a particular approved method of use. *Id.* at 40a. Judge Dyk further explained that, when the counterclaim provision was enacted in 2003, FDA had already "adopted detailed requirements for the submission of 'patent information' for both drugs and methods," including use codes, *id.* at 33a, and "Congress was well aware of this regulatory interpretation of 'patent information' when it enacted the counterclaim provision," *id.* at 36a. Judge Dyk therefore would have read the term "patent information" in the counterclaim provision to encompass the "method of use" information at issue in this case. *Id.* at 39a.

d. The court of appeals denied rehearing en banc with two judges dissenting. Pet. App. 53a-56a.

5. The district court subsequently held the '358 patent invalid for obviousness and unenforceable for inequitable conduct before the Patent and Trademark Office. Br. in Opp. App. 14a. Respondents' appeal from that judgment has been stayed pending this Court's decision in this case. *Novo Nordisk A/S* v. *Caraco Pharm. Labs., Ltd.*, No. 2011-1223 Docket entry (Fed. Cir. July 27, 2011).

SUMMARY OF ARGUMENT

A. The text and context of the counterclaim provision show that it authorizes an ANDA applicant to challenge an NDA holder's overbroad use code.

1. An ANDA applicant can obtain an order requiring the NDA holder "to correct or delete * * * patent information * * * on the ground that the patent does not claim either (aa) the drug for which the application was approved; or (bb) an approved method of using the drug." 21 U.S.C. 355(j)(5)(C)(ii)(I). Because respondents represented to FDA that the '358 patent claims a method of using repaglinide, subsection (bb) applies here. Respondents contend that, so long as the patent claims some approved method of use—here, use of repaglinide in combination with metformin—subsection (bb) is unavailable. Petitioner argues that the '358 patent "does not claim * * * an approved method of using the drug" because it does not claim the use of repaglinide for monotherapy, the approved use for which petitioner seeks carve-out labeling under section viii. Petitioner is correct.

Petitioner's reading preserves more natural and distinct roles for the terms "correct" and "delete" in the

counterclaim provision than does respondents' interpretation. And by allowing "correct[ion]" of overbroad use codes, petitioner's reading allows the counterclaim provision to facilitate the section viii process, thereby preventing inaccurate or imprecise Orange Book listings from impeding FDA approval of generic drugs. Respondents' reading, by contrast, disregards the role of the counterclaim provision within the statutory framework and forecloses judicial relief no matter how great the disparity between the NDA holder's use code and the patent's actual coverage.

2. The remedy available through the counterclaim provision—an "order requiring the [NDA holder] to correct or delete the patent information submitted by the holder under [21 U.S.C. 355(b) or (c)]"—encompasses the remedy petitioner seeks here. In particular, the "patent information" that can be "correct[ed]" includes a use code. That use code is "patent information" both in the ordinary sense and in the sense FDA used the phrase in the 2003 rulemaking that set the stage for Congress's enactment of the counterclaim provision. And that use code was "submitted" by respondents "under"—that is, in a proceeding governed by—the referenced statutory sections governing NDAs.

B. Respondents' narrow interpretation of the counterclaim provision would undermine the Hatch-Waxman scheme.

1. The Hatch-Waxman Amendments were designed to achieve a balance between creating incentives that foster drug innovation and promoting competition that benefits consumers. Starting in the late 1990s, NDA holders had upset that balance by submitting to FDA inappropriate patent information that prevented or delayed generic competitors from entering the market.

The counterclaim provision enacted in 2003 provides a judicial mechanism to remedy such abuses. Petitioner's invocation of the counterclaim provision here protects the Hatch-Waxman balance in the way Congress envisioned.

2. In respondents' view, the counterclaim provision authorizes judicial enforcement of some of FDA's patent-listing requirements (in particular, FDA rules specifying that certain types of patents should not be listed at all), but not others (of relevance here, FDA's determination that an NDA holder should submit a use code that identifies specifically the approved uses claimed by a method-of-use patent). That distinction makes little sense. Both types of regulatory violation involve an NDA holder's submission of incorrect or misleading patent information; both exploit FDA's lack of resources, authority, or expertise to police patent claims; and both can delay or obstruct a generic drug's entry into the market. The concerns that prompted Congress to enact the counterclaim provision are therefore directly and fully implicated here.

ARGUMENT

In respondents' view, a brand-name manufacturer can prevent or delay generic competition by submitting to FDA an overbroad description of its method-of-use patent. Congress enacted the counterclaim provision, however, to combat precisely that sort of manipulation. The text and context of the provision show that it provides a remedy under the circumstances petitioner alleges here. Reading the counterclaim provision in the constricted way respondents propose would impair ANDA applicants' ability to secure FDA approval for their products, subvert Congress's effort to create a

meaningful judicial check on NDA holders' exaggerated claims of patent protection, and deprive consumers of the full benefit of generic competition.

A. The Text And Context Of The Counterclaim Provision Show That It Authorizes A Challenge To An Overbroad Use Code

The court of appeals made two errors in parsing the counterclaim provision. First, it read the provision to require a showing that a method-of-use patent listed in the Orange Book does not claim *any* "approved method of using" an approved drug. In fact, the text and context of the provision indicate that, even if a brand-name manufacturer's patent covers *some* approved method of using the drug, a counterclaim can be asserted if the NDA holder's use code falsely or misleadingly describes the patent's scope in a way that blocks approval of a generic equivalent for other approved uses that the patent does not claim. Second, in considering whether a remedy was available to petitioner, the court of appeals gave an unduly narrow reading to the phrase "patent information submitted by the [NDA] holder under [21 U.S.C. 355(b) or (c)]." Use codes are literally "patent information," and by regulation they are "submitted * * * under" the specified subsections.

1. a. The counterclaim provision states that an ANDA applicant can obtain relief "on the ground that the patent does not claim either (aa) the drug for which the application was approved; or (bb) an approved method of using the drug." 21 U.S.C. 355(j)(5)(C)(ii)(I). The phrase "on the ground that" indicates that subsections (aa) and (bb) state the exclusive bases on which the district court can "requir[e] the [NDA] holder to correct or delete the [Orange Book] patent information." *Ibid.*;

see *Black's Law Dictionary* 772 (9th ed. 2004) (defining "ground" as "the reason or point that something * * * relies on for validity"). By the time the counterclaim provision was enacted in 2003, "the FDA had adopted detailed requirements for the submission of 'patent information' for both drugs and methods." Pet. App. 33a (Dyk, J., dissenting). Those regulations and accompanying forms require each NDA holder or applicant, with respect to each patent listed in the Orange Book, "to identify whether the submitted patent claims a 'drug substance,' 'drug product,' or 'method of use.'" *Id.* at 36a; see pp. 8-9, *supra*.

When an NDA holder has identified a particular patent as claiming a drug substance or drug product (and thus does not assert that the patent claims a method of using the drug), an ANDA applicant who wishes to challenge that listing can rely on subsection (aa) of the counterclaim provision to assert that the patent does not claim "the drug for which the application was approved." The counterclaimant might contend, for example, that the patent actually claims a metabolite of the drug. See p. 8, *supra*. When the NDA holder identifies a patent as a method-of-use patent (and thus does not assert that the patent claims the drug itself), an ANDA applicant can invoke subsection (bb) of the counterclaim provision to allege that the patent does not claim "an approved method of use." The counterclaim provision is thus best understood as authorizing the would-be generic manufacturer to respond to the NDA holder's description of its own patent by asserting that the patent does not claim either the approved drug or an approved method of use, *as the case may be*.

b. In their revised Orange Book use code, respondents described Claim 4 of the '358 patent as claiming

"[a] method for improving glycemic control in adults with type 2 diabetes mellitus." Pet. App. 9a. Because respondents described their patent as claiming an approved method of use rather than the drug itself, petitioner's challenge to the Orange Book listing turns on the proper interpretation of subsection (bb) of the counterclaim provision. Respondents contend that, so long as the patent claims *some* approved method of use—here, use of repaglinide in combination with metformin—subsection (bb) is unavailable, even if their use code misleadingly suggests that the patent claims other approved methods of use as well. Petitioner argues that the '358 patent "does not claim * * * an approved method of using the drug" because it does not claim use of repaglinide for monotherapy, the approved use for which petitioner seeks carve-out labeling under section viii. Petitioner is correct.

First, petitioner's interpretation preserves distinct roles for the terms "correct or delete" in the counterclaim provision. Under respondents' view, an Orange Book listing of a method-of-use patent can be successfully attacked only if the patent does not claim *any* approved method of use. But if an ANDA applicant can make that showing, the patent should not be listed in the Orange Book at all, and the listing should accordingly be "delete[d]." The word "correct," by contrast, naturally covers situations where a particular method-of-use patent is appropriately listed in the Orange Book, but the use code submitted by the NDA holder falsely or misleadingly describes the method(s) of use that the patent claims. Thus, an NDA holder's use code may be judicially "correct[ed]" if the counterclaimant identifies an approved method of use that is encompassed by the use

code but that the patent does not actually claim. See Pet. App. 40a (Dyk, J., dissenting).

Second, respondents' argument disregards the role of the counterclaim provision within the larger statutory framework. See, *e.g.*, *Davis* v. *Michigan Dep't of Treasury*, 489 U.S. 803, 809 (1989) (explaining that individual statutory provisions "must be read in their context and with a view to their place in the overall statutory scheme"). The section viii process, which long predated the 2003 enactment of the counterclaim provision, was specifically designed to ensure that an NDA holder's patent on *one* approved method of use did not foreclose the marketing of generic drugs for *other*, unpatented approved methods. In its 2003 rulemaking, moreover, FDA expressly linked its new patent-information requirements to the section viii process. The agency explained that it was requiring more specific information on method-of-use patents in order to enable ANDA applicants and FDA more accurately to "determine whether the applicant * * * may submit a section viii statement." 68 Fed. Reg. at 36,682; see p. 9, *supra*.

The purpose of the counterclaim provision was to afford a judicial remedy when inaccurate or imprecise Orange Book listings impede FDA approval of generic drugs. And subsection (bb) of the counterclaim provision makes clear that Congress specifically contemplated the provision's application to method-of-use patents. Allowing judicial "correct[ion]" of overbroad method-of-use listings ensures that the counterclaim provision can facilitate the section viii process, thereby furthering the objectives that FDA sought to achieve when it required more precise method-of-use information. As applied to method-of-use patents, the counterclaim provision would fail to serve its intended purpose

in an important category of cases if it could be invoked only when a listed patent claims no approved method of use at all.[2]

The general fact pattern involved in this case, in which an NDA holder's method-of-use patent remains in effect well after the patent on the drug itself has expired, is a common one. To prevent such patents from foreclosing generic competition with respect to *unpatented* uses, and thus effectively extending the NDA holder's monopoly on the approved drug, it is essential that Orange Book listings accurately and precisely describe the methods of use that NDA holders' patents claim. See Pet. App. 71a-72a (district court opinion). Under respondents' reading of the counterclaim provision, however, judicial relief is unavailable no matter how great the disparity between the NDA holder's use code and the patent's actual coverage. Respondents' reading thus invites an NDA holder to exploit a patent claiming one approved use of a drug to block generic competition in all other approved uses of the drug. To the extent the counterclaim provision is ambiguous, it should be construed to avoid that untoward result.

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[2] The court of appeals underappreciated the relevance of the statutory context because it "detect[ed] no ambiguity in the statutory language." Pet. App. 12a. But the court's reasoning—that "standard grammar generally provides that 'a' means 'any,'" *ibid.*—is mistaken. Context often informs whether "a" means "one" or "any." For example, when spoken to someone holding four tennis rackets, the statement "if you are not using a racket, I'd like to practice my serve" is naturally interpreted as asking whether *one* racket is not in use, while the statement "if you are not using a racket, my family would like to play doubles" is naturally interpreted as asking whether *any* rackets are in use.

2. The court of appeals also held that the counterclaim was unavailable to petitioner because the remedy it prescribes—"an order compelling 'the [NDA] holder to correct or delete the patent information submitted by the holder'"—did not encompass the correction of a use code. Pet. App. 15a-17a. The court construed the term "patent information" in the counterclaim provision to be limited to "the patent number and the expiration date." *Id.* at 15a.[3] That is mistaken.

a. A use code is "patent information" within any usual understanding of that term because it is "information"—a "description of the patented method of use," 21 C.F.R. 314.53(c)(2)(ii)(P)(3)—about a "patent." Use codes are also properly characterized as being "submitted * * * under subsection (b) or (c) of this section" (*i.e.*, 21 U.S.C. 355(b) or (c)). Sections 355(b) and (c) describe the entire process for seeking and obtaining approval for an NDA. In that context, "under" is best read to mean "in a proceeding subject to or governed by" Sections 355(b) and (c). *Cf. Ardestani* v. *INS*, 502 U.S. 129, 135 (1991) (reaching similar conclusion); *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661, 666-667 (1990) (construing a Hatch-Waxman provision that refers to "submission of information *under* a Federal law" to "suggest[] [a submission] in furtherance of or compli-

[3] Based on its understanding of the term "patent information," the court of appeals concluded that "the counterclaim provision only authorizes suits to correct or delete an erroneous patent number or expiration date." Pet. App. 15a-16a. But the counterclaim provision does not authorize the court to order correction or deletion of patent information "on the ground that" the patent number or expiration date listed in the Orange Book is incorrect. Rather, subsections (aa) and (bb) of the counterclaim provision state the exclusive grounds on which the court can order patent information to be corrected or deleted. See pp. 18-19, *supra*.

ance with a comprehensive scheme of regulation"). The patent information encompassed by the counterclaim provision (*i.e.*, the information "submitted * * * under" Sections 355(b) and (c)) thus includes everything FDA requires NDA holders to submit in the course of seeking and maintaining approval of an NDA—including the use code at issue here.

Respondents would limit "patent information submitted * * * under subsection (b) or (c)" to "patent information described in" those subsections. Resp. C.A. Br. 24. To be sure, the only patent information that Sections 355(b) and (c) *require* to be submitted is the patent number and expiration date. But the counterclaim provision does not refer to patent information "described in" or "required by" or "prescribed by" Sections 355(b) or (c). Other provisions within Section 355, by contrast, do use such language. See 21 U.S.C. 355(d)(6) (directing FDA to refuse to approve an NDA if "the [NDA] failed to contain the patent information *prescribed by* subsection (b) of this section") (emphasis added); see also 21 U.S.C. 355(e)(4) (using same phrasing in identifying grounds for withdrawing NDA approval). Because "[t]he use of different terms within related statutes generally implies that different meanings were intended," *United States* v. *Bean*, 537 U.S. 71, 76 n.4 (2002) (citation omitted), the word "under" in the counterclaim provision reaches beyond the patent information expressly referenced in Sections 355(b) and (c).

b. The regulatory backdrop against which Congress enacted the counterclaim provision in 2003 reinforces the natural reading of the statutory language. Earlier that year, FDA had promulgated regulations specifying what "patent information" an NDA applicant must submit. Pet. App. 16a (citing 21 C.F.R. 314.53). Those reg-

ulations, entitled "Submission of Patent Information," require an NDA applicant to submit descriptions of the uses claimed by its method-of-use patents. 21 C.F.R. 314.53(c)(2)(i)(O) and (ii)(P); see 68 Fed. Reg. at 36,703. The accompanying forms for submitting that information to FDA state that information on the forms is "provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355(b) and (c)]." 68 Fed. Reg. at 36,707, 36,710.[4]

Similarly, FDA regulations in effect since 1994 precluded an ANDA applicant from submitting a section viii statement if it sought approval for an indication that, "according to the patent information submitted under section 505(b) or (c) of the act [21 U.S.C. 355(b) or (c)] and [21 C.F.R] 314.53[,] * * * is claimed by a use patent." 21 C.F.R. 314.94(a)(12)(iii)(B). Thus, FDA has always understood the patent information listed in 21 C.F.R. 314.53—which as of 2003 included use codes—to be "submitted under section 505(b) or (c) of the act [21 U.S.C. 355(b) or (c)]."

"Congress was well aware of this regulatory interpretation of 'patent information' when it enacted the counterclaim provision." Pet. App. 36a (Dyk, J., dissent-

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[4] Relying on FDA's Federal Register notice regarding Office of Management and Budget clearance of the forms used for submitting patent information, respondents contend that FDA "require[s] use code narratives under its general rulemaking authority and [21 U.S.C. 355](j)." Br. in Opp. 27 (citing 72 Fed. Reg. 21,268-21,269 (2007)). But the forms refer to Sections 355(b) and (c), not Section 355(j). 68 Fed. Reg. at 36,707, 36,710. More fundamentally, respondents' argument conflates the *manner* in which the patent information is provided to FDA (as part of an NDA submitted under 21 U.S.C. 355(b) and (c)) with the *reason* the patent information is needed ("for effective implementation of the patent certification and 'section viii statement' provisions," 72 Fed. Reg. at 21,268).

ing) (discussing pertinent legislative history). Indeed, the purpose of the counterclaim provision was to authorize judicial enforcement of FDA's recently expanded requirements governing Orange Book listings. There is consequently no sound reason to suppose that the "patent information" to which the counterclaim provision refers is more limited than the "patent information" that FDA requires NDA holders to submit. See *id.* at 37a-38a & nn.11-12 (citing cases).

B. An Unduly Narrow Reading Of The Counterclaim Provision Would Undermine The Hatch-Waxman Scheme

Respondents' narrow interpretation of the counterclaim provision would frustrate Congress's purposes. Properly understood, that provision protects the Hatch-Waxman scheme's balance between encouraging brand-name manufacturers to develop and market new drugs and facilitating the entry of generic drugs that promote competition.

1. The counterclaim provision protects the Hatch-Waxman Amendments' balance between innovation and competition

The Hatch-Waxman Amendments were designed to achieve a balance between, on the one hand, fostering drug innovation by providing NDA holders a reasonable period of exclusivity and, on the other hand, promoting competition that benefits consumers by facilitating the timely entry of generic drugs. The time required to secure FDA approval—both initially for an NDA and later for an ANDA—can significantly affect the length of the NDA holder's exclusivity. See *Eli Lilly*, 496 U.S. at 671-672; p. 6, *supra*. In particular, the time needed to obtain approval for a generic version of a drug can "create an effective extension of the patent term" for the NDA

holder. *Eli Lilly*, 496 U.S. at 670. The Hatch-Waxman Amendments address that issue in part through the streamlined ANDA process, 21 U.S.C. 355(j)(1)-(4); in part by authorizing generic manufacturers to begin developing their drugs before the conclusion of the patent term without risking an infringement suit, 35 U.S.C. 271(e)(1); and in part by delaying ANDA approval only while a limited set of patent infringement issues are resolved in litigation, 21 U.S.C. 355(j)(5)(B).

As the Federal Trade Commission (FTC) found in its 2002 study, however, NDA holders had upset the Hatch-Waxman balance by submitting a host of inappropriate patent information to FDA that prevented or delayed FDA's approval of ANDAs, thereby delaying the entry of generic competitors and effectively extending NDA holders' periods of exclusivity. See p. 7, *supra*. The 2003 amendments were designed to restore the balance and facilitate the timely approval of generic drugs. See 149 Cong. Rec. at 15,515 (statement of Sen. Schumer) ("What our proposal does is encourages robust competition by allowing the generic to come on to the market in its fair time. It restores the balance of Hatch-Waxman.").

The root weakness that NDA holders were exploiting was FDA's need to rely unquestioningly on the patent information they submitted, even though NDA holders have an obvious incentive to overstate the scope of their patents. Shortly before the counterclaim provision was enacted, FDA had issued a final rule "clarif[ying] patent submission and listing requirements," which would, FDA expected, "reduce confusion and help curb attempts to take advantage of this process." 68 Fed. Reg. at 36,676. FDA explained, however, that because it lacks the expertise and resources to resolve questions of

patent law, it would be unable to evaluate the accuracy of NDA holders' patent listings and use codes. See pp. 9-10, *supra*. FDA acknowledged that NDA holders could "submit inappropriate patent information * * * to delay generic competition." 68 Fed. Reg. at 36,683. But it explained that "[a] fundamental assumption of the Hatch-Waxman Amendments is that the courts," not FDA, "are the appropriate mechanism for the resolution of disputes about the scope and validity of patents." *Ibid.*[5]

Embracing FDA's approach, Congress stepped in to supply the necessary mechanism for judicial resolution of disputes over patent information. See 149 Cong. Rec. at 31,200 (statement of Sen. Schumer) ("[T]he provisions enforce the patent listing requirements at the FDA by allowing a generic applicant * * * to file a counterclaim to have the brand drug company delist the patent or correct the patent information in FDA's Orange Book."). In channeling such disputes to the courts, Congress structured the new remedy exclusively as a counterclaim to existing patent infringement litigation. See 21 U.S.C. 355(j)(5)(C)(ii)(II). Although Congress might have made the remedy marginally more available to ANDA applicants by creating a freestanding cause of action, the counterclaim approach has several virtues. Because the counterclaim can be invoked only when a generic manufacturer genuinely seeks to market the

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[5] The only administrative mechanism for deleting or correcting patent information entails FDA forwarding inquiries about patent information to the NDA holder, which retains discretion to maintain or alter its patent information. 21 C.F.R. 314.53(f). While this procedure can suffice to correct clerical errors, it was not intended to provide a mechanism for resolving substantive patent disputes, which require judicial resolution.

drug and a brand-name manufacturer asserts that doing so would infringe its patent, it will not embroil courts in abstract disputes over patent information. By consolidating all the litigation surrounding the drug and related patents, the counterclaim provision also ensures that the judge will be familiar with the issues and avoids potentially conflicting constructions of the patent from different courts. See 149 Cong. Rec. at 15,517 (statement of Sen. Gregg) (new bill "will not open up a whole new arena of litigation" but will instead operate "in the context of the already existing causes of action").

2. Respondents' interpretation of the counterclaim provision would frustrate Congress's purposes

In respondents' view, the counterclaim provision authorizes judicial enforcement of some of FDA's patent-listing requirements (such as FDA's determination that "patents claiming packaging, intermediates, or metabolites must not be submitted for listing," 68 Fed. Reg. at 36,676), but not others (of relevance here, FDA's determination that an NDA holder should submit use codes that "identify *specifically* the approved uses claimed by the method-of-use patent," *id.* at 36,682 (emphasis added)). That distinction cannot be squared with Congress's purposes in enacting the counterclaim provision. Respondents' approach is especially unwarranted because both types of regulatory violation involve an NDA holder's submission of incorrect or misleading patent information; both exploit the same weakness in the administrative scheme (FDA's lack of resources, authority, or expertise to engage in substantive review of patents); and both cause the same harm (unjustified delay or obstruction of a generic drug's entry into the market) to

the same victims (the ANDA applicant and, ultimately, consumers).

Respondents posit that "[t]he counterclaim was a congressional response to *Mylan Pharms., Inc.* v. *Thompson*, 268 F.3d 1323 (Fed. Cir. 2001) [cert. denied, 537 U.S. 941 (2002)]." Resp. Supp. Br. 5-6. In *Mylan*, an ANDA applicant alleged that an NDA holder's patent should not have been listed in the Orange Book at all, and the Federal Circuit held that no judicial remedy for that assertedly improper listing was available under the pre-2003 statutory scheme.[6] Respondents contend that the counterclaim is available *only* to an entity that "finds itself in the same position as Mylan was in *Mylan*." *Ibid.*

Mylan was surely significant to Congress in that it established the gravity of the problem: an ANDA applicant was powerless to contest the accuracy or precision of patent information submitted by an NDA holder. But it does not follow that Congress aimed only to avoid *Mylan* redux. Even if "the decision in [*Mylan*] prompted the *proposal* of [the counterclaim provision]."

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[6] In *Mylan*, after marketing the anti-anxiety drug buspirone for many years, the NDA holder (Bristol) obtained a patent claiming the use of a metabolite of buspirone to treat anxiety. Bristol submitted this patent to FDA for listing in the Orange Book and represented that the patent claimed a method of using buspirone. *Mylan*, 268 F.3d at 1327-1328. The ANDA applicant (Mylan) then "sought a declaratory judgment that Bristol improperly listed the * * * patent, and a preliminary injunction requiring Bristol to take steps to delist the * * * patent." *Id.* at 1328. Mylan conceded there was no cause of action to enforce FDA's patent-listing requirements against Bristol. The Federal Circuit agreed, and it further held that a declaratory judgment action was unavailable because improper listing of the patent in the Orange Book would not have been a defense to an infringement suit by Bristol against Mylan in response to a paragraph IV certification by Mylan. *Id.* at 1329-1333.

"whether that alone accounted for its *enactment* is quite a different question." *Eli Lilly*, 496 U.S. at 670 n.3. For several reasons, respondents' argument should be rejected.

First, FDA had recognized in its 2003 rulemaking that, even when an NDA holder's method-of-use patent is entitled to be listed in the Orange Book, FDA's ability to administer the Hatch-Waxman scheme depends on precise and accurate information about the particular method(s) of use that the patent covers. The 2003 rule's requirement that each NDA holder "identify specifically the approved uses claimed by [its] method-of-use patent" enables FDA and ANDA applicants to "determine whether the applicant must submit a patent certification or may submit a section viii statement." 68 Fed. Reg. at 36,682; see pp. 4-5, 9-10, *supra*. At the same time, however, FDA made clear that it would "rely on the description of the approved use provided by the NDA holder." 68 Fed. Reg. at 36,682. "[S]tatutory prohibitions often go beyond the principal evil to cover reasonably comparable evils." *DePierre* v. *United States*, 131 S. Ct. 2225, 2235 (2011) (citation omitted). By foreclosing generic competition that FDA might otherwise have approved pursuant to a section viii statement, the submission of overbroad use codes can cause substantially the same ill effects as does Orange Book listing of patents that should not be listed at all, and FDA's lack of resources and patent expertise prevents the agency from adequately policing either type of abuse. The concerns that prompted Congress to enact the counterclaim provision are therefore directly and fully implicated here.

Second, if Congress had intended the counterclaim provision to serve the limited purpose that respondents posit, it could have authorized the court simply to order

that an improper listing be "delete[d]." Congress instead authorized judicial orders "requiring the [RLD NDA holder] to *correct or* delete the patent information submitted by the holder." 21 U.S.C. 355(j)(5)(C)(ii)(I) (emphasis added). The italicized language is naturally read to cover the situation in which a method-of-use patent is appropriate for listing in the Orange Book, but the NDA holder's submission overstates the range of approved uses that the patent covers. See p. 20, *supra*.

Third, even if the counterclaim provision had not been enacted, an ANDA applicant in Mylan's situation could make a paragraph IV certification to the relevant patent, accept the 30-month stay of approval provided by 21 U.S.C. 355(j)(5)(B)(iii), and litigate the question whether its generic drug would infringe the patent. But when an ANDA applicant alleges that an NDA holder's use code is overbroad, paragraph IV litigation cannot substitute for the counterclaim provision. A paragraph IV certification cannot be premised on proposed carve-out labeling. Cf. 59 Fed. Reg. 50,347 (1994). Rather, to submit a paragraph IV certification, the ANDA applicant must propose labeling the same as the RLD's, and must assert that the RLD NDA holder's patent "is invalid or will not be infringed" (21 U.S.C. 355(j)(2)(A)(vii)(IV)) even if the generic manufacturer uses that labeling. So long as the NDA holder's patent covers *some* approved method of using the approved drug, the proposed labeling will be infringing. See Pet. App. 50a (Dyk, J., dissenting). The court in paragraph IV litigation therefore will have no occasion to determine whether carve-out labeling could allow generic competition without infringing the NDA holder's method-of-use patent, or whether the use code submitted by the NDA holder accurately and precisely de-

scribes the method of use claimed in the patent. The practical need for the counterclaim provision is therefore even greater in the present context than in the *Mylan* scenario.

Fourth, the use-code issue is of substantial practical importance, and there is no reason to believe that Congress thought it could be safely ignored. FDA approval of carve-out labeling based on section viii statements is an important path to market entry for generic drugs. FDA has informed us that in Fiscal Year 2010, it approved 11 sets of ANDAs with carve-out labeling. And of the five top-selling brand-name drugs that "went generic" for the first time during that period, three of the corresponding ANDAs relied on a section viii statement. Indeed, the top two brand-name drugs that went generic—each with annual sales of approximately $2.5 billion—did so with carve-out labeling. Because the use of carve-out labeling depends on the accuracy and precision of NDA holders' use codes, an important aspect of the Hatch-Waxman balance would be subverted if the counterclaim provision were unavailable in this context.

* * *

For the foregoing reasons, the judgment of the court of appeals should be vacated, and the case should be remanded for further proceedings. Because the court of appeals incorrectly held that petitioner had no cause of action to challenge respondents' use code for the '358 patent, it did not pass on the district court's determination that respondents' use code misleadingly described the method of use claimed in the patent. That case-specific question should be left to the court of appeals in the first instance.

CONCLUSION

The judgment of the court of appeals should be vacated and the case remanded for further proceedings.

Respectfully submitted.

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SEPTEMBER 2011

AMICUS CURIAE BRIEF

No. 10-844

In the Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES AND SUN PHARMACEUTICAL INDUSTRIES, LTD.
PETITIONERS,
v.
NOVO NORDISK A/S AND NOVO NORDISK, INC.,
RESPONDENTS.

ON WRIT OF CERTIORARI
TO THE UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

BRIEF FOR AARP AND U.S. PIRG AS *AMICI CURIAE* IN SUPPORT OF PETITIONERS

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INTERESTS OF *AMICI CURIAE*[1]

Amicus Curiae AARP is a nonpartisan, nonprofit organization dedicated to addressing the needs and interests of people aged fifty and older. AARP has a long history of advocating for access to affordable health care and for controlling costs without compromising quality. Affordable prescription medication is particularly important to the older population which, because of its higher rates of chronic and serious health conditions, has the highest rate of prescription drug use. Persons over sixty-five, although only thirteen percent of the population, account for thirty-four percent of all prescriptions dispensed and forty-two cents of every dollar spent on prescription drugs. Families USA, *Cost Overdose: Growth in Drug Spending for the Elderly*, 1992-2010 at 2 (July 2000), *available at* http://famil iesusa2.org/assets/pdfs/drugod852b.pdf. Significantly, in a 2005 AARP survey, one in four Americans, ages 50 and older, who took a prescription drug in the past five years said they did not fill a prescription written by their doctor in the past two years. Cost was reported as the main deterrent. Linda L. Barrett, Ph.D., AARP, *Prescription Drug Use Among Midlife and Older*

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[1] The parties have consented to the filing of this brief. Pursuant to Rule 37.6, *amici curiae* state that no counsel for a party wrote this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person or entity other than *amici curiae* has made a monetary contribution to this brief's preparation or submission.

Americans (2005), *available at* assets.aarp.org/rg center/health/rx_midlife_plus.pdf. Since prescription drug spending has skyrocketed over the last decade and a half, and national health expenditures on prescription drugs have quadrupled, AARP advocates for broader access to prescription drugs and lower prescription drug costs for consumers. *See e.g.*, AARP, *Rx Watchdog Report*: Brand Name Drug Prices Continue to Climb Despite Low General Inflation Rate, May 2010, *available at* http://www.aarp.org/health/medicare-insurance/info-04-2009/rx_watchdog.html. (AARP, *Rx Watchdog Report*).

Amicus Curiae U.S. PIRG (Public Interest Research Group) is a federation of 28 non-profit, non-partisan state Public Interest Research Groups. The PIRGs have worked on behalf of American consumers since 1970 for a fair and competitive marketplace, a sustainable economy, and a responsive, democratic government. Its staff of policy experts, researchers, organizers, and advocates have authored reports, generated media coverage, organized citizens, and lobbied in the state and federal legislatures winning important victories in the areas of consumer protection, public transportation, product safety, health care, and good government. U.S. PIRG is supported by contributions from its tens of thousands of citizen members, and also receives significant funding from foundation grants. It has long advocated for safer, more affordable prescription drugs, and promoted the availability of generic alternatives to brand-name medicines.

SUMMARY OF ARGUMENT

The American healthcare system is in turmoil. Costs continue to rise while access to care continues to shrink, leaving millions of Americans wondering how they are going to obtain the care they require. This is especially true for pharmaceuticals. For at least the past fifteen years, the increase in prescription drug costs has outpaced other healthcare costs. Kaiser Family Foundation, *Prescription Drug Costs: Background Brief, available at* http://www.kaiseredu.org/Issue-Modules/Prescription-Drug-Costs/Background-Brief.aspx (Fe b. 2010). During the period of highest average annual increase, from 1995-2002, the pharmaceutical manufacturing industry was the single most profitable industry in the United States. *Id.*

The Drug Price Competition and Patent Term Restoration Act of 1984, colloquially known as the Hatch-Waxman Act, provides a solution to the growing concern of pharmaceutical costs and prevent the very situation in which we find ourselves today. Pub. L. No. 98-417, 98 Stat. 1585. The original Hatch-Waxman Act established the abbreviated new drug application (ANDA) process. ANDA sought to strike a balance between the pharmaceutical industry's need for continued innovation, the pharmaceutical manufacturers' desire to capitalize on their efforts and protect their work through the patent system, and the public's interest in affordable healthcare.

Through ANDA, generic manufacturers may bypass submissions of independent clinical testing

by showing that the generic drug contains the same active ingredients and is bioequivalent to a brand pharmaceutical already on the market. 21 U.S.C. § 355 (j)(2)(A)(ii) and (iv). The Act further protect the brand pharmaceutical manufacturers by requiring ANDA applicants to carry the burden of showing how the proposed generic drug will not infringe upon any of the patents held by the brand bioequivalent drug. 21 U.S.C. § 355(j)(2)(vii)-(viii). The Food and Drug Administration (FDA) maintains the *Approved Drug Products with Therapeutic Equivalence Evaluations*, colloquially referred to as the "Orange Book." Among the information collected in the Orange Book is a "description of the patented method of use as required for publication." 21 C.F.R. § 314.53(c)(2)(ii)(P). There is, however, no oversight regulating brand manufacturers' accurate representation of their method of use patents in the Orange Book. The FDA's interaction with the Orange Book is "solely ministerial." Fed. Trade Comm'n, *Generic Drug Entry Prior to Patent Expiration: An FTC Study*, v (July 2002), *available at* http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf (Fed. Trade Comm'n, *Generic Drug Entry*).

Notwithstanding the Hatch-Waxman Act, prescription drug prices continued to escalate. Despite the intent of the legislation to incentivize and facilitate generic entry, loopholes, ambiguities, and procedural gamesmanship prevented most generics from using the ANDA process as Congress intended. Most notably, brand pharmaceutical companies learned to amend their method of use patent information to expand the scope of protection

and duration, even when the patent did not in fact protect this enlarged scope. This strategy affects not only generic manufacturers that seek to compete directly with the patent holder, but also generic manufacturers seeking "carve out" approval through a section viii statement. 21 U.S.C. § 355(j)(2)(A)(viii). A section viii statement allows a generic version of a drug to be used through a method of use that is not protected by the underlying patent. A generic may only receive a carve-out labeling if it is completely different from the Orange Book listing. Thus, when a brand manufacturer provides an all-encompassing description of its method of use patent, a generic has no opportunity to bring the drug to market, despite the fact that the brand does not use the drug in the manner proposed by the generic.

Congress recognized the shortcomings of the ANDA system, and enacted the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, § 1101(a)(2)(C), 117 Stat. 2066, 2452 (codified at 21 U.S.C. § 355(j)(5)(C)(ii). This Amendment allows a generic ANDA applicant to assert a counterclaim against a brand to "correct or delete the patent information submitted by the holder" under the Hatch-Waxman Act. A valid patent holder can delay the entry of a generic for 30 months by filing a patent infringement claim within 45 days of learning about an ANDA application, unless a court determines that the patent is invalid or not subject to infringement. 21 U.S.C. § 355(j)(5)(B)(iii). This, however, is not true for section viii applications, since the ANDA

application claims not to infringe. 21 U.S.C. § 355 (j)(5)(B)(i)-(iii). A misreading of the counterclaim provision led the Federal Circuit Court to conclude that the counterclaim is only available when the patent at issue does not claim any approved method of using the drug. Simply put, as long as a brand manufacturer has a method of use patent that covers at least one approved use, the counterclaim provision provides no recourse for a generic ANDA application forestalled from market entry.

The narrative today focuses on whether brand pharmaceutical manufacturers will be able to again thwart the efforts of Congress and the Food and Drug Administration to facilitate and expedite the entry of generic pharmaceuticals on the market. As it stands with the Federal Circuit Court's holding, a brand pharmaceutical manufacturer will always be able to further delay any generic ANDA application by 30 months so long as it has a viable method of use patent, even if that method of use patent is not at all related to the ANDA application. This has dramatic effects on the American consumer, who realizes the full benefits of generics in the marketplace only when there is competition between brands and generics, and between generics themselves. By circumventing the counterclaim provision through manipulation of inaccurate method of use codes, brand manufacturers are directly harming millions of consumers by denying them the benefits of generic drugs and thereby imposing unreasonably high costs on healthcare.

ARGUMENT

Following the rationale of the Federal Circuit, a brand manufacturer can prevent competition from a generic competitor by submitting a method use patent description that overstates the actual scope of the patent. The Federal Circuit's opinion is especially puzzling because the counterclaim provision in question was enacted to address this very harm. The legislative history of the 2003 Amendment verifies this intention, as sponsor Senator Charles Schumer explained "[t]he provisions close loopholes in the law and end the abusive practices in the pharmaceutical industry which have kept lower-priced generics off the market and cost consumers billions of dollars....[t]he provisions enforce the patent listing requirements at the FDA by allowing a generic applicant, when it has been sued for patent infringement, to file a counterclaim to have the brand drug company delist the patent or correct the patent information in the Orange Book." 149 Cong. Rec. 31200 (Nov. 23, 2003) (statement of Sen. Schumer). The addition of the counterclaim provision sought to end, once and for all, the practice of brand manufacturers evading generic entry by engaging in Orange Book trickery.

Perhaps overlooked in this battle between powerful pharmaceutical companies is the importance of generic drugs to the American consumer, both directly and indirectly. It is no surprise that brand name drugs are more expensive than their generic counterpart – in fact the average brand medication cost $1880 more than the average

generic medication over a twelve-month period ending in 2010. AARP, *Rx Watchdog Report*.

Consumers are harmed in two distinct ways from this ruling. First, the misreading of the counterclaim provision ensures a prolonged monopoly for brand manufacturers – including for uses never considered or not patented by the brand – which protracts higher prices and limits choice on the market. Direct consumers of this particular drug, and the tax-paying citizenry at large, both suffer when paying these higher prices. Second, sanctioning this pernicious activity further emboldens brand manufacturers to game the system, by devising new ways to prevent generics from succeeding. This in turn disincentivizes generic manufacturers from entering the market at all. Thus, the Federal Circuit opinion, if left intact, virtually insures compounded consumer harm through higher prices and less choice over both the short and the long-term.

I. The Federal Circuit Opinion Undermines the Effort of the Hatch-Waxman Act to Combat Escalating Health Care Costs

The purpose of the Hatch-Waxman Act, and subsequent Medicare Amendments, is clear. The Federal Trade Commission explained that the Hatch-Waxman Act "established a regulatory framework that sought to balance incentives for continued innovation by research-based pharmaceutical companies and opportunities for market entry by generic drug manufacturers." Fed.

Trade Comm'n, *Generic Drug Entry*. Perhaps Judge Dyk best articulated the importance of the Hatch-Waxman Act and subsequent 2003 amendment in his dissent: "Congress enacted the counterclaim provision of the Hatch-Waxman Act in order to prevent manipulative practices by patent holders with respect to the Orange Book listings. These practices were designed to delay the onset of competition from generic drug manufacturers . . . the majority . . . construes the statute contrary to its manifest purpose." *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd*, 601 F.3d 1359, 1368-69 (Fed. Cir. 2010).

Healthcare costs are alarmingly high, and generic drugs provide an opportunity for consumers to receive the care they need at a more affordable price. When generics are precluded from avenues for market entry, the anticipated market effects will not occur, and consumers will suffer. The harmful effects are felt both by direct purchasing consumers, as well as the citizenry as a whole.

A. Generic Pharmaceuticals Are Vital To Providing Affordable Health Care to Millions of Consumers

It is unquestionable that the presence of generics that successfully navigate the ANDA system results in lower prices. The National Association of Chain Drug Stores estimates that a generic version of a drug is 76% less than the brand price. U.S. Dept. of Health and Human Services, *Expanding the Use of Generic Drugs*, December 2010, *available at*

http://aspe.hhs.gov/sp/reports/2010/GenericDrugs/ib.shtml (HHS, *Expanding the Use of Generic Drugs*). Savings continue to amass as more generics enter for a particular drug. *Id.* The Generic Pharmaceutical Association estimates that the use of generics has saved the entire healthcare industry $139.6 billion in 2009 alone, and up to $824 billion over the past decade. Generic Pharm. Ass'n., *Savings Achieved Through the Use of Generic Pharmaceuticals 2000-2009*, July 2010, *available at* http://gphaonline.org/sites/default/files/GPhA%20Savings%20Study%20Book%20Updated%20Web%20FINAL%20Jul 23%2010_0.pdf.

There are three pathways through which generic drugs reduce healthcare costs. First, generics may serve as a direct substitute for the original branded drug. The generic manufacturer does not enjoy the same monopoly power that the brand enjoyed, and does not have the same research and development costs to recoup. Second, generics make therapeutic substitution more viable. Consumers benefit either by paying a lower price for a particular treatment or by having access to treatments that might have otherwise been unavailable. Third, the presence of generics in the marketplace forces brands to lower their prices. Even if a consumer chooses to forego the opportunity to purchase generics, their mere presence in the marketplace ensures that brand prices will come down. *Id.*

The totality of these factors represents considerable benefits for consumers, either through savings or increased choice. The Hatch-Waxman Act

strives to ensure that benefits not only persist, but also expand. The lost savings from precluded generics is likely to be exacerbated in the coming years, as numerous high-profile and widely distributed drugs are set to come off patent by 2015. *See* Melly Alazraki, *The 10 Biggest-Selling Drugs That Are About to Lose Their Patent*, Daily Finance, (Feb. 27, 2011), *available at* http://www.dailyfinance.com/2011/02/27/top-selling-drugs-are-about-to -lose-patent-protection-ready/.

Even a thirty month delay in the access to generic versions of previously patented drugs will cost the consumer base billions of dollars. The ANDA process and the counterclaim provision are absolutely vital to ensuring that the system operates as designed. However, if the Federal Circuit's opinion stands, it is a virtual certainty that the manufacturers in charge of these drugs and others will exploit the loophole and prolong their monopoly beyond the expiration dates.

B. The United States Government, as a Market Participant, Also Benefits Significantly From Generic Entry

Consumers also benefit indirectly when healthcare prices decrease. The Congressional Budget Office (CBO) estimated in 2007 that purchasing generic drugs under Medicare Part D resulted in savings of approximately $33 billion. Congressional Budget Office, *Effects of Using Generic Drugs on Medicare's Prescription Drug Spending*, Sept. 2010, at 18, *available at*

http://www.cbo.gov/ftpdocs/118xx/doc11838/09-15PrescriptionDrugs.pdf. Furthermore, the CBO also projects that the federal government would save another $14 billion through 2012 if generic substitutes become available for those drugs that will lose their patent protection during that time. *Id.* at 18-19. This data does not account for therapeutic substitution which might occur as more generics enter the market, which the CBO projects to provide an additional savings of at least $4 billion. *Id.* at viii.

The gamesmanship of brand manufacturers prevents government healthcare programs the opportunity to use generic alternatives at significant savings to the taxpayers. This harm occurs at the end of a cycle of sole manufacturing and distribution rights for the brands. The ANDA process is well-balanced to ensure that proper incentives remain with the brand manufacturers to compel future innovation. The law does not and should not provide these manufacturers with the opportunity to demand higher prices for artificially extended periods merely by misrepresenting their patent information to a government body compelled to obey this information but powerless to verify it.

II. If Left Unchecked, the Federal Circuit's Opinion Will Render ANDA Ineffective and Jeopardize the Viability of Generic Manufacturers

It has been established that brand manufacturers will deploy any number of strategies to undermine

the economic viability of generic manufacturers. Tactics such as knowingly supplying false use codes have two pernicious effects on the market. First, the pharmaceutical industry is certain to see an increase in incorrect use codes. More incorrect and overbroad use codes will only stall the eventual entry of those generics poised to enter the market. Second, when taken as an industry practice, the strategy has the long-term effect of dissuading generic manufacturers from entering the marketplace at all.

A. The Practice of Patent Use Code Abuse Inappropriately Stalls the Entry of Generic Drugs and Is Certain to Become More Prevalent as Manufacturers Learn How to Exploit the Loophole

If Respondent is successful in thwarting Petitioners' attempts at bringing its generic to market, all brand manufacturers will follow suit. Soon, all NDAs in the Orange Book will have method of use patents covering the entire array of potential applications. Use codes are already becoming more prevalent. Ten years ago there were 360 total use codes in the Orange Book. Today there are over 1,000, and the number is only growing. See Kurt R. Karst, Analysis Shows Patent Use Codes Have Doubled Since August 2003 (July 8, 2010), *available at* http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2010/07/analysis-shows-patent-use-codes-have-doubled-since-august-2003--by-kurt-r-karst-http.wwwhpmcomvattorneycfmrid22.html.

Limiting the effectiveness of ANDA would devastate the generic pharmaceutical industry, which would ultimately further burden consumers. ANDA functions by providing a 180 day window of exclusive generic status to the first ANDA to successfully complete the process. This window serves as an incentive for generic manufacturers to compete in the creation of generic drugs. Once the 180 day window expires, all generics may obtain FDA approval. It is at this stage that the consumer reaps the greatest benefit from the program. HHS, *Expanding the Use of Generic Drugs*.

Investors agree. Brand manufacturers are likely to employ the patent use code strategy to stall generics from entering the market moving forward. *See* Morgan Stanley Research Europe, *Pharmaceuticals: Potential Selective Upside for Industry Post Prandin Ruling* 2 (Sept. 1, 2010), *available at* http://www.fdalawblog.net/files/Morgan stanley-rpt---puc-decision.pdf. This is a very profitable maneuver for the brand pharmaceutical industry, and a very threatening reality for generics. Unless courts intervene and curb this tactic, brands simply will continue to exploit the loophole unabashedly.

Adding insult to injury in this case is the brazen nature in which Respondent admits that Petitioners' method of use would not infringe upon its patent. Respondent is flaunting the loophole in front of all, showing that even legislation specifically enacted to achieve the opposite result is no match for the brand

pharmaceutical industry's ability to expand and prolong its patents.

B. Generic Manufacturers Will be Dissuaded From Pursuing ANDA Status as Brand Manufacturers Continue to Devise Methods to Block Generic Entry

In this case, Petitioners' diligence in developing a generic version of repaglinide will certainly lead to lower costs for those suffering from diabetes. Despite Respondent's tactics, there now exists a generic version that will, at some point, drive down the cost. The question for Petitioners is when it will see a return on its investment. But the question for consumers is whether they will see a continued commitment by the generic manufacturing industry to develop generic drugs. It is possible that rulings such as the Federal Circuit's will lead to a diminished interest by generic developers, as the risk of failing to capitalize on diligence may prove too costly to embark on the journey of creating the generic.

This Court is uniquely able to rectify this mistake. The FDA is powerless to change its approach, especially with the controlling authority of the Federal Circuit providing a myopic interpretation of the counterclaim provision. The FDA has long conceded that the courts are the most appropriate vehicle for interpreting the Hatch-Waxman Act, having explained a "fundamental assumption of the Hatch-Waxman [Act] is that the courts are the

appropriate mechanism for the resolution of disputes about the scope and validity of patents." 68 Fed. Reg. 36683 (2003). Reciprocally, federal courts have acknowledged that the FDA does not closely monitor compliance with the Orange Book, a fact that results in fraud and misrepresentation. One court explained, "we have no reason to believe that because applicants are *supposed* to submit information about approved uses only, they *in fact* do so." *Purepac Pharm. Co. v. TorPharm, Inc.*, 354 F.3d 877, 884 (D.C. Cir. 2004).

Furthermore, Congress has already spoken on this issue. The enactment of the 2003 Amendments was a clear signal to the FDA and courts that the counterclaim provision was necessary to stop the abusive tactics of brand manufacturers. As current FDA Assistant Chief Counsel Julie Dohm once noted, "The FDA's *Orange Book* restriction conflicts with both of the stated purposes of the Hatch-Waxman Act, and would confer substantial additional rights on pioneer drug patent owners that Congress quite clearly did not intend to confer." Julie Dohm, *Expanding the Scope of the Hatch-Waxman Act's Patent Carve-Out Exception to the Identical Drug Labeling Requirement: Closing the Patent Litigation Loophole*, 156 U. Pa. L. Rev. 151, 182 (2007). It is time to once and for all provide the judicial remedies conferred by Congress to generic manufacturers so that they can defend their rights under the Hatch-Waxman Act, and strike the balance that Congress initially envisioned nearly thirty years ago.

CONCLUSION

Because the Federal Circuit's opinion misreads the law, abrogates the legislative intent, impermissibly extends the scope of a patent, and threatens the wellbeing of consumers through artificially increased prices and limited choice, this Court should reverse the Federal Circuit.

Respectfully submitted,

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AMICUS CURIAE BRIEF

No. 10-844

IN THE
Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD. AND SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Petitioners.

v.

NOVO NORDISK A/S AND NOVO NORDISK INC.,
Respondents.

On Writ of Certiorari to the
United States Court of Appeals for the Federal Circuit

BRIEF OF AMICI CURIAE ALLERGAN, INC., SHIRE PHARMACEUTICALS, INC., MEDICIS PHARMACEUTICAL CORP., AND SOMAXON CORP. IN SUPPORT OF RESPONDENTS

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INTEREST OF AMICI CURIAE INNOVATOR PHARMACEUTICAL COMPANIES[1]

Amici Curiae are so-called "innovator" or "branded" pharmaceutical companies. Collectively, *amici* and companies similarly situated to *amici* invest tens of billions of dollars annually on the research and development of new drugs, as well as new indications and uses for "old" drugs. The latter is a growing and increasingly important area of interest for pharmaceutical manufacturers, physicians and patients.

Through exhaustive and expensive clinical research, the branded pharmaceutical industry has been able to discover new indications and "re-purpose" old drugs to eliminate and/or reduce the occurrence and effects of serious diseases and illnesses. This research involves substantial risks. The reward for taking these risks is patent protection on the newly discovered indications, without which innovator companies would be unable to recoup their investments.

The Hatch-Waxman Act and the 2003 amendments to it take into account these risks and rewards and carefully balance the interests of innovator pharmaceutical companies with the

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[1] Pursuant to Rule 37.6, *amici* certify that no counsel for a party authored this brief in whole or in part and that no person or entity, other than *amici* or its counsel, has made any monetary contribution to the preparation or submission of this brief. The parties have consented to the filing of this brief. A letter acknowledging consent by petitioners accompanies this brief, and respondents have filed a letter with the Clerk of the Court providing blanket consent to the filing of *amicus* briefs.

interests of their generic competitors. Caraco, and the *amici* in support of a reversal of the Federal Circuit's decision (collectively, "Caraco"), propose a reading of 21 U.S.C. § 355 that threatens, not furthers, this balance. Caraco attempts to circumscribe the process set forth in the statute and delay method of use patent infringement inquiries until *after* generic drugs come on to the market, when the market for the innovator product has already been destroyed by the generic product. It does this by taking a construct of the FDA, namely Orange Book use codes, and conflating it with the carefully constructed "pre-launch" patent protection scheme established under the Act. This is contrary to the Act's language and purpose, whose patent provisions are designed to resolve such disputes *before* the generic is launched.

In addition to being contrary to the Act's purpose, the relief requested by Caraco is likely to cause satellite litigation in every pharmaceutical method of use patent case surrounding the wording chosen by the branded manufacturer for its Orange Book use codes. Rather than the simple, administrative tools they were designed to be, use codes may come to look like patent claims that will have to be interpreted by FDA in the context of drug labeling. As all parties and *amici* agree, FDA is ill equipped to assess patent claims and their scope or to make infringement decisions about generic drugs.

Accordingly, the undersigned innovator pharmaceutical companies respectfully urge this Court to affirm the Federal Circuit's decision.

SUMMARY OF ARUMENT

The Federal Circuit correctly held that "the terms of the counterclaim provision do not authorize an order compelling the patent holder to change its use code narrative." *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 601 F.3d 1359, 1366 (Fed. Cir. 2010), *cert. granted (mem.)*, 131 S. Ct. 3057 (U.S. June 27, 2011) (No. 10-844). This is so not only for the reasons and support found in the Federal Circuit's opinion, but also, because the "use code" is a creation of the FDA, and not of the Hatch-Waxman Act or Congress. For FDA purposes, use codes are used as regulatory surrogates for actual patent claims. Properly viewed, they allow FDA to render summary decisions on the scope of generic ANDA applicant's request for approval as an adjunct to, not replacement of, the notice and litigation procedures carefully laid out in the Hatch-Waxman Act.

Unlike the objective patent information required by statute (patent number and expiration date), use codes required by regulations are highly subjective and thus, not easily addressed by courts under the counterclaim provisions. Indeed, if Caraco were correct that it and/or any generic could ask a court to enjoin a patent holder to change the "use code" for an approved dug product, use codes would begin to look like patent claims. FDA would then need to evaluate if and how these patent claim-like use codes relate to approved indications and generic ANDA applicants' proposed labels. This is not a task that FDA is equipped to undertake.

Use codes are not patent claims. They are approved indications covered by patent claims. They are provided to FDA and subsequently published in

the Orange Book. They are not, nor are they intended to be, legally determinative of infringement. Caraco seeks to change this in an effort to avoid the Hatch-Waxman protections by carving out the approved use specifically claimed in an unexpired patent, obtaining FDA approval while bypassing the statutory provisions requiring patent certification and notice to the innovative pharmaceutical company pre-launch, and heading to market with a generic drug that is substitutable for ***all*** indications, including those that infringe the unexpired patent. This has the potential to render valueless method of use patents covering newly discovered indications, strongly dis-incentivizing innovator pharmaceutical companies from the pursuit of additional uses for safe and effective drugs. Surely, such a glaring "loophole" in Hatch-Waxman's pre-launch patent protection scheme is not what Congress intended.

Further, Caraco's argument that a properly drafted "use code" would allow generic entry more swiftly is based on an incorrect reading of the statute. As the plain language of the statute makes clear, every ANDA is required to contain a patent certification "and" a section viii statement when the latter is applicable, i.e., where there is a listed method of use patent that does not claim or cover every approved indication, for each Orange Book listed patent. Congress did not intend for generics to simply bypass the procedure for method of use patents' certifications by "carving out" approved uses, particularly when approved generics are adjudged therapeutically equivalent to the branded drug product by FDA, and are thus fully substitutable for the branded product, regardless of the narrower label of the generic. Method of use patents listed in the

Orange Book, regardless of use codes, should be treated the same as compound and formulation patents where patent certifications alleging non-infringement are required. There is no cogent reason why method of use patents need not be certified and infringement not considered pre-launch via the mechanism set forth by the Hatch-Waxman Act. At a minimum, this issue needs further study by the Court of Appeals before the "use code" counterclaim issue should be decided.

ARGUMENT

A. Finding New Uses For "Old" Drugs Is A Critical Area Of Emerging Innovation

Caraco argues that branded pharmaceutical companies have overstepped appropriate boundaries or "manipulated" the Hatch-Waxman Act by the conduct at issue in this case. Nothing could be further from the truth. As explained below, it is generic companies that have overstepped and improperly taken advantage of the section viii provisions in the statute. Contrary to the Hatch-Waxman Act's language and purpose, generic companies are "carving out" patented uses from their labels, securing approval of such so-called "skinny labels", and then receiving from FDA so-called "A" ratings, which allow their products to be substituted for not just the un-patented use for which the generic drug received approval, but also for the patented use that the generic has "carved out" from its label. Terry G. Mahn, *Skinny Labeling and the Inducement of Patent Infringement*, UPDATE, Nov./Dec. 2010, at 39. As a consequence, generic drug companies effectively receive the benefit of having the patented

use on the label without paying the price of having to defend a pre-market case for patent infringement under the Hatch-Waxman Act.

This situation highly dis-incentivizes innovator pharmaceutical companies from researching and pursuing approval of new indications for previously approved drugs. The discovery of new indications and uses for old drugs should be encouraged, not discouraged by a crabbed reading of the Hatch-Waxman Act that conflates an FDA construct – "use codes" – with infringement determinations in a court of law.

The research and development costs for bringing a new drug to market are estimated to be $1.3 billion. Ted Agres, *New Life for Old Drugs*, DRUG DISCOVERY & DEVELOPMENT, Aug. 1, 2011, *available at* http://www.dddmag.com/article-New-Life-for-Old-Drugs-72911.aspx. It often takes 10-15 years to bring a new drug to market. *Id.* And, there is a slim rate of success – 5%. *Id.* Drug repurposing, i.e., finding a new indication for an old drug, is a way of lowering these costs of drug development and getting new therapies to patients more quickly. Amy D. Marcus, *Researchers Show Gains in Finding Reusable Drugs*, WALL ST. J., August 18, 2011, *available at* http://online.wsj.com/article/SB10001424053111903639404576514542144726276.html?. More specifically, costs and failure rates are reduced as the starting point is often an already approved compound with established safety and bioavailability profiles, proven formulation and manufacturing routes, and well-characterized pharmacology. As a result, these compounds can enter clinical trials more

quickly and receive FDA approval on a more expedited basis.

New uses of old drugs have been recognized as "a growing area of interest" and " as a way of lowering costs of drug development and getting therapies to patients more quickly." Marcus, *supra*. As the National Institute of Health (NIH) has explained, drug repurposing allows "[e]xpansion of a drug's clinical use to new indications." Christopher P. Austin et al., *The NCGC Pharmaceutical Collection: A Comprehensive Resource of Clinically Approved Drugs Enabling Repurposing and Chemical Genomics*, 80 SCIENCE TRANSLATIONAL MEDICINE, April 27, 2011, at 1. And, while "many examples exist of successful repurposing, only recently has the concept of large-scale, even comprehensive, examination of the disease applications of clinically used drugs been considered." *Id.* at 10.

Examples of drug repurposing include Requip® (ropinorole) and Mirapex® (pramipexole), manufactured by GlaxoSmithKline and Boehringer-Ingelheim, respectively. Initially, both of these drugs were approved for use solely in Parkinson's disease. Extensive further research led to the development of these drugs for use in restless leg syndrome (a disease affecting 8% of the population). Sara H. Sleigh & Cheryl L. Barton, *Repurposing Strategies for Therapeutics*, 24 PHARMACEUTICAL MEDICINE 151, 153 (2010).

Another oft-cited example of an innovator pharmaceutical company repurposing an "old" drug is the revitalization of thalidomide by Celgene in the United States. Thalidomide was originally prescribed in the 1950s for nausea and insomnia in

pregnant women. It caused severe birth defects and was taken off the market in 1961. In a surprising 1965 article, an Israeli doctor reported that thalidomide alleviated complications of leprosy. Jacob Sheskin, *Thalidomide in the Treatment of Lepra Reactions*, 6 CLINICAL PHARMACOLOGY & THERAPEUTICS 303–06 (1965). It was also later discovered that thalidomide had antiangiogenic and immunomodulatory effects. Agres, *supra*. These findings prompted an innovator company, Celgene, to risk the capital required to secure approval from the FDA of new uses of the previously banned Thalidomide. Celgene was successful and received approval from FDA to market Thalomid® (thalidomide) as a treatment for leprosy in 1998. Since its approval, Thalomid® has become a flagship product for Celgene, now with an additional indication for multiple myeloma. In addition, through controlled clinical trials and FDA compassionate-use programs, the drug has been found to be effective in treating a myriad of disorders, including certain mycobacterial and autoimmune diseases, HIV and AIDS-related afflictions, and cancer.

Simply put, these kinds of new uses for drugs will not be developed by innovator pharmaceutical companies without the ability to enforce patent rights on the new methods of use. Bringing these new uses to market is very expensive (only 40% less than the new drug), and FDA exclusivities related to them (three years only, *see* 21 C.F.R. § 314.108

(2010))[2], provide only limited value. Agres, *supra*. "While the FDA will give market exclusivity for a new indication, there is little to prevent physicians from prescribing a generic version in its place." *Id.* As a result, as Atul Butte, M.D., Ph.D., assistant professor of medicine at Stanford University School of Medicine noted "[h]ighlighting new uses for off-patent drugs may be exciting, but it is a challenge for companies to get enough value out of it to fund clinical trials . . . . It's an unanswered question right now." According to Drug Discovery & Development, it is a question to which the National Institute of Health (NIH) is seeking to help answer with an initiative to find ways to make "repurposing more practical and less burdensome." *Id.*

B. "Use Codes" Are Constructs Of The Food & Drug Administration, Not Statutory Requirements

Section 505 of the Hatch-Waxman Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355), regulates the approval process for drugs in the United States. As part of this approval process, innovator pharmaceutical companies filing a New Drug Application ("NDA") are required to identify all patents and their

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[2] When a drug is approved for a new indication, Hatch-Waxman provides for three years of so-called "label exclusivity." Pub. L. No. 98-417, § 101, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355(j)(5)(F)(iv)). Unlike the exclusivities for newly-discovered molecules, this type of exclusivity does not stop a generic manufacturer from filing an ANDA during the period of the exclusivity (though FDA could not approve it). *Id.* Because it can take years to recover the investment required to undertake patient clinical trials and obtain FDA approval for any new use, 3 years of data exclusivity is simply inadequate for recouping these investments. Patent protection is essential.

respective expiration dates that claim the drug or an approved method of using the drug. *See* 21 U.S.C. §§ 355(b)–(c).

Under the FDA's authority to promulgate regulations for the efficient enforcement of this statute, the FDA separately requires an innovator pharmaceutical company to submit Form 3542 to the FDA identifying the patent number and the expiration dates of any applicable patents. If a patent claims one or more approved methods of using the drug, Form 3542 also requires "a description of the approved indication or method of use" also known as the "use code." *See* Form FDA 3542: Patent Information Submitted Upon and After Approval of an NDA or Supplement 3 (rev. Oct. 2010), *available at* http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048345.pdf. The FDA publishes a list of approved drugs, along with applicable patents and any associated use codes in its Approved Drug Products With Therapeutic Equivalence Evaluation, *i.e.*, the Orange Book.

Nowhere in the statute or legislative history of the Hatch-Waxman Act are use codes and descriptions required. This is hardly surprising given that use codes are intended to compliment the patent information provided to FDA by branded manufacturers and published in the Orange Book. Use codes are designed to give notice to both FDA and interested generic drug companies of the patents the innovator pharmaceutical company believes cover uses that have been approved by FDA. *See* Applications for FDA Approval to Market a New Drug, 68 Fed. Reg. 36,676, 36,683 (June 18, 2003) ("Use codes are intended to alert ANDA and 505(b)(2)

applicants to the existence of a patent that claims an approved use.").

"Use codes" were thus not intended to be debatable, or as Caraco requests – *litigious* – issues. If the brand's assertion, through its use code, that a particular method of use was approved turned out to be erroneous, the counterclaim provision of Hatch-Waxman, as it already existed, would take care of the problem. A generic applicant could seek de-listing of the patent as not covering an approved use, and that would be the end of it. 21 U.S.C. § 355(j)(5)(C)(ii)(I) (2006) (permitting a "counterclaim seeking an order requiring the [patent] holder to correct or delete information submitted by the holder ... on the ground that the patent does not claim ... an approved method of using the drug"). As use codes were envisioned by FDA, there is no need to litigate them.

Indeed, litigating over the particular words of a use code will result in a quagmire and will create a flurry of satellite litigations that are not in the courts' or the public's interest. FDA currently accepts the use code submitted by the innovator company and publishes it in the Orange Book. Its role in this regard is ministerial. Applications for FDA Approval to Market a New Drug, 68 Fed. Reg. at 36,683. (FDA stated that "it is more efficient and accurate" to ask the NDA holder to provide "the exact use code description to be published in the Orange Book." *Id.* FDA further said that "[i]n addition to the absence of any statutory basis for a substantive agency review of patents, we have long observed that we lack expertise in patent matters. . . . [O]ur patent listing role remains ministerial." *Id.*).

If Caraco's relief is granted, a permissible counterclaim to change the "use code" description will first be filed with a court. If the counterclaim is successful, the innovator will be directed to change the published use code. But, to what? It is only by happenstance that, in the case at bar, there is another use code to adopt if Caraco is successful – namely, the original use code that Novo had submitted. In most cases, however, that will simply not be the case. A brand will properly list a patent in the Orange Book and provide its use code to the FDA, which will adopt it. That will be all that there is. If a generic company then challenges that use code in Court as insufficiently descriptive of a patent, unlike in the case at bar, there will not be an alternative use code to adopt. Either the district court will have to re-write the use code, or FDA will. Neither is in an appropriate position to do so.

Further, if that happens, the innovator pharmaceutical company will appeal immediately. As the appeal is pending, and there is potential loss of the Hatch-Waxman's Act 30-month stay of approval on the generic's proposed drug product (provided by Congress so that any patent infringement issues would be litigated pre-launch), FDA will need to become less "ministerial" and compare the new use code to the carved out indication, making a substantive determination as to whether the two are commensurate in scope and if the carve-out is allowable under section viii. This is not a determination FDA is equipped to make. Moreover, the innovator company may concurrently file a citizen's petition with FDA arguing that the carve-out should not be allowed. The unsuccessful

party before FDA on that issue may then sue FDA in district court. Further appeals will likely follow.

But despite the inevitable number of court and FDA proceedings sparked by these counterclaims and potential changes to use codes, none will address patent infringement. In fact, the patent infringement issue will take a back seat to determining the propriety of certain "use code" language: only after resolution of the "use code" issues, will patent infringement cases proceed. *See e.g., AstraZeneca LP v. Apotex, Inc.*, 623 F. Supp. 2d 579 (D.N.J. 2009). This is inefficient and a waste of the courts' and parties' resources, and, is inconsistent with Hatch-Waxman. Satellite litigations, like those inevitable under Caraco's requested relief, can and should be avoided.

C. Because Label Carve-Outs Result In Infringement of the Very Patents That Are Designed to Be Carved Out, Limiting the Counterclaim to Whether a Patent Is Properly Listed Is Appropriate

While the general rule that a generic drug must be labeled for the same conditions of use as the approved innovator drug is skirted when carve-out labels are approved, the same cannot be said for infringement liability. This is so because despite FDA's rules permitting drugs to be marketed only for approved uses—i.e., in the context of a generic "carve-out," the non-patented use—the drugs may still be prescribed, dispensed and used in an infringing manner. In fact, most are.

This is a result of FDA's therapeutic equivalence rating and generic substitution practices. When a

generic drug is approved by the FDA it receives a therapeutic equivalence rating of A or B. Mahn, *supra*. The "A" code, which is most commonly given, indicates that the generic is therapeutically equivalent to the branded product; products receiving such code can be "***substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the [branded] product***." Drugs@FDA Glossary of Terms, http://www.fda.gov/Drugs/informationondrugs/ucm079436.htm#T (last updated Jan. 7, 2010) (defining "therapeutic equivalence (TE)") (emphasis added). There is no limitation of this therapeutic equivalence to any particular approved use.

While state laws and regulations vary in their approach to the management of generic drug substitution, in practice, pharmacists in nearly every state use these "A" ratings in the Orange Book as the primary basis for generic drug substitution determinations. Mahn, *supra*. In fourteen states, pharmacies are required to substitute "A"-rated generics for branded prescriptions (unless prescribing physician indicates no substitution). *Id.* All other states have laws or regulations that leave the selection of equivalent generic drugs completely to the discretion of the pharmacists making the substitution decisions. *Id.* Pharmacists and personnel on the boards of pharmacy routinely rely on "A"-rated generics listed in the Orange Book when making those substitution decisions. *Id.*

Despite these substitution practices, the pharmacist, prescribing physician and/or patient often have no idea what uses are approved on an A-rated generic. This is not surprising as there is no

compendium tracking or publishing such information. The consequence is that generics approved by FDA with labels carving out certain methods of use are treated identical to generics that did not carve out those uses (as well as the branded product). As a result, in the case at bar, there can be no dispute that Caraco's proposed generic drug will be prescribed and dispensed for the use it proposes to carve out. This is so even though Caraco will technically not have approval for that use.

The approval process and substitutability of generic ANDAs with carve-outs already disincentivizes branded manufacturers from developing new uses of old drugs. This would worsen if the patent counterclaim provision is not narrowly construed. If a patent is listed properly in the Orange Book, a dispute over a use code should not be the gate-keeper to whether or not litigation over the patent should be allowed to proceed.

D. The Hatch-Waxman Act's Policy of Resolving Patent Disputes Before Market Launch Supports The Federal Circuit's Decision

As the Federal Circuit correctly found, permitting Caraco to counterclaim for a narrower use code is contrary to the central policy aim of the Hatch-Waxman Act, *i.e.*, to strike a balance between the interests of generic and innovator manufacturers. *Novo*, 601 F.3d at 1364–65.

The Hatch-Waxman Act was intended to promote innovation by innovator pharmaceutical companies while also promoting early and efficient access to generic drugs. *See Prepared Statement of the FTC Regarding Competition in the Pharmaceutical*

Industry Before the S. Comm. on Judiciary, 108th Cong. (2003) (statement of Timothy J. Muris, Chairman, Fed. Trade Comm'n), *available at* http://www.ftc.gov/os/2003/06/030617pharmtestimony.htm. The Act specifically permits generic drug companies to partially circumvent patent restrictions and accelerate FDA approval so that they can bring generic products to market as soon as the innovator drug companies' patents expire or are found invalid or not infringed. *See* 35 U.S.C. § 271(e); *see also Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 675–78 (1990).

Before the Act, generic drug manufacturers would be liable for infringement of viable innovator patents under 35 U.S.C. § 271(e) by actions such as seeking approval of proposed generic drug products. The Act, however, created a safe harbor provision whereby generic drug manufacturers no longer have to wait until the expiration of the branded drug patents to begin their development of a generic drug product and/or to begin the abbreviated drug approval process. This provision significantly reduced the amount of time for generic entry. *Id.*

One of the "*quid pro quos*" of this so-called "safe harbor" in Hatch-Waxman is the patent litigation provisions of the statute. These provisions generally provide that, if a generic manufacturer wishes to challenge an innovator patent, that process will play out before the generic product comes to market. Integral to this process is the 30-month stay on approval that results when the generic applicant provides a paragraph IV certification and the branded company files a lawsuit within 45 days. By so doing, the branded company is afforded a single

opportunity to litigate the challenged patents without fear of having its market destroyed – i.e., before the generic company comes to market. This is only fair since it is the branded company that has invested in the patented product and the generic company seeks to copy it. *See generally* Robin J. Strongin, *Hatch-Waxman, Generics, and Patents: Balancing Prescription Drug Innovation, Competition, and Affordability* (Nat'l Health Policy Forum, Background Paper, 2002), *available at* http://www.nhpf.org/library/background-papers/BP_HatchWaxman_6-02.pdf.

While Caraco and its *amici*, including the government, deride this 30-month stay as causing delay; that is the point of it. The generic company receives the benefit of a safe harbor provision partaking in infringing activities while copying the branded drug without having to face an infringement suit until later. Moreover, the reality is that the 30-month stay does not delay anything. This time period coincides with the average time for FDA approval of an ANDA, causing little to no delay before the generic drug gets to market. *See* K.L. Spear M.D., President, Spear Pharmaceuticals and GPHA Board member, Comments at the FDA Public Meeting on Generic Drug User Fees (Sept. 17, 2010), *available at* http://www.fda.gov/downloads/Drugs/NewsEvents/UCM226833.pdf.

The resolution of any infringement claims prior to the generic drug products launch was a clear intention of the Act as it encourages the development of new drugs and the protection of valid patents. In fact, courts have recognized that, in pharmaceutical cases like this, "the incentive for discovery and

development of new products [would be] adversely affected" by "shifting market benefits to the infringer while litigation is pending for patents that are likely to withstand the attack." *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1362 (Fed. Cir. 2008).

Indeed, if a generic drug is permitted to enter the market before even consideration of patent infringement issues, the financial hardship falls on the innovator pharmaceutical company alone and the balance created by the Act is no longer maintained. In effect, the generic gets all the benefits of the Act – including the ability to rely on the innovator's research, data and creation of the market – without paying any of the price.

Market research has shown that generic drugs typically capture approximately 80-90% of the prescriptions of the branded drug within six months of the generic's launch. FED. TRADE COMM'N, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION 12 (2009). The loss of market share for branded companies occurs very quickly and often can never be regained. Moreover, it results in significant changes to the branded company including loss of jobs and research and development monies. These losses are irreparable. *See e.g., Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1362 (Fed. Cir. 2008) (finding loss of revenue and market share caused by generic entry constitutes irreparable harm); *Bio-Technology Gen. Corp. v. Genentech, Inc.*, 80 F.3d 1553, 1566 (Fed. Cir. 1996) (finding that loss of revenue, goodwill, and research and development support constitute irreparable harm); *see also AstraZeneca LP v. Apotex, Inc.*, 623 F. Supp. 2d 579, 612 (D.N.J. 2009) (finding that "the damage caused

by a loss in personnel and the impact this would have on the company are indeed significant and unquantifiable").

For example, in *Pfizer, Inc. v. Teva Pharmaceuticals, USA, Inc.*, 429 F.3d 1364, 1382 (Fed. Cir. 2005), the Federal Circuit affirmed the district court's grant of a preliminary injunction enjoining the sale of an infringing generic drug, noting that "while the statutory framework . . . does seek to make low cost generic drugs available to the public, it does not do so by entirely eliminating the exclusionary rights conveyed by pharmaceutical patents. Nor does the statutory framework encourage or excuse infringement of valid pharmaceutical patents."

Further, the public interest favors protecting valid patents by preventing premature entry of generic drugs into the market. The mere "selling [of] a lower priced product does not justify infringing a patent. Were that to be a justification for patent infringement, most injunctions would be denied because copiers universally price their products lower than innovators." *Payless Shoesource, Inc. v. Reebok Int'l Ltd.*, 998 F.2d 985, 991 (Fed. Cir. 1993); *see also Pfizer*, 429 F.3d at 1382. Indeed, in the pharmaceutical industry, the public policy is best served by protecting patent rights in order to encourage investment in research and development:

> Although companies . . . which do not engage in significant amounts of research and development, consequently might be able to undercut the prices offered by pharmaceutical manufacturers that devote large sums to invention and product

> improvement, this type of short-term competition does not, at least in the considered opinion of the Congress, serve the public interest. Instead, Congress has determined that it is better for the nation in the long-run to afford the inventors of novel, useful, and nonobvious products short-term monopolies on such products than it is to permit free competition in such goods.

Eli Lilly & Co. v. Premo Pharm. Labs., Inc., 630 F.2d 120, 138 (3d Cir. 1980).

Significantly, FDA has already shown that it is ill-equipped to resolve disputes ahead of time through its application of section viii: FDA has permitted section viii carve-outs that have resulted in infringement. For example, in *AstraZeneca LP v. Apotex, Inc.*, 623 F. Supp. 2d 579 (D.N.J. 2009), Apotex submitted an ANDA referencing AstraZeneca's drug Pulmicort Respules and "carved out" the patented method of use covering once-daily administration. FDA approved the ANDA based on the section viii statement, i.e., "carve out," and Apotex launched its generic product. One day later, AstraZeneca filed a declaratory judgment action and a motion for a preliminary injunction on the grounds that, among other things, the generic drug and its proposed label would induce users to infringe the patented method covering once daily administration despite the "carve-out" by Apotex. The district court found for AstraZeneca. The Federal Circuit affirmed. *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042 (Fed. Cir. 2010). This case confirms that patent infringement remains a separate inquiry from whether a carve-out is appropriate on a generic label;

it also demonstrates that FDA does not have the capacity to render reliable decisions on patent scope and infringement.

Caraco's position in this case will perpetuate cases such as *AstraZeneca* by asking FDA to make determinations that are better left to the patent holder and the courts. Leaving the counterclaim provision out of the use code quagmire will leave approval of drug products to FDA and patent issues to district courts. This Court should reject Caraco's argument and keep the regulatory scheme promulgated by FDA separate from patent inquiries.

E. Underlying This Case is FDA's Erroneous "Either/Or" Policy, Which, in Violation of the Statute, Invites Carved Out Indications In Lieu Of Patent Certifications

A generic drug manufacturer seeking approval for a generic drug product files an Abbreviated New Drug Application ("ANDA") and the requirements for its application are governed by 21 U.S.C. § 355(j) (2006).

Relevant to the instant case is the statutory requirement for an ANDA to contain:

> (vii) ***a certification***, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the listed drug referred to in clause (i) or which claims a use for such listed drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (c) of this section—

(I) that such patent information has not been filed,

(II) that such patent has expired,

(III) of the date on which such patent will expire, or

(IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; ***and***

(viii) if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, ***a statement*** that the method of use patent does not claim such a use.

21 U.S.C. §§ 355 (j)(2)(A)(vii)–(viii) (2006) (emphasis added).

The plain language of the statute thus requires ***both*** a certification ***and*** a section viii statement when the ANDA applicant is seeking approval for a use not claimed by the method of use patent. Nowhere in its language does the statute imply that a section viii statement can replace the certification required by 21 U.S.C. §355 (j)(2)(A)(vii); *see also* H.R. REP. NO. 98-957, pt. 1, at 22 (1984).

This reading is further confirmed by the legislative history: "if there are indications which are claimed by any use patent and for which the applicant is not seeking approval, then an ANDA must state that the applicant is not seeking approval

for those indications which are claimed by such use patent. For example, the listed drug may be approved for two indications. ***If the applicant is seeking approval only for Indication No. 1, and not Indication No. 2 because it is protected by a use patent, then the applicant must make the appropriate certification and a statement*** explaining that it is not seeking approval for Indication No. 2." H.R. REP. NO. 98-957, pt. 1, at 22 (1984) (emphasis added).

The House Report further clarifies that an ANDA cannot be approved if it is missing any of the elements required under § 505(j)(2)(A) and gives as an example, a missing patent certification, thereby indicating that a certification is needed in all ANDAs. *Id.*[3]

FDA policy diverges from the statute's clear language and legislative intent. Specifically, it ignores the term "and" and implements and an "either/or" policy treating sections vii and viii as mutually exclusive.

This FDA policy was addressed in *Purepac Pharmaceutical Co. v. Thompson*, 238 F. Supp. 2d 191 (D.D.C. 2002), *aff'd* 354 F.3d 877 (D.C. Cir. 2004), and *TorPharm, Inc. v. Thompson*, 260 F. Supp. 2d 69 (D.D.C. 2003) *aff'd by Purepac Pharm. Co. v. Thompson*, 354 F.3d 877 (D.C. Cir. 2004). *See also Warner-Lambert Co. v. Apotex Corp.*, No. 98-C-

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[3] Section viii of the statute requires ANDA applicant to inform FDA how and why the proposed generic label will differ from the innovator product label. FDA relies on this information to assess the label and indications for which the generic is seeking approval without having to assess patents and claims.

4293, 2001 WL 1104618 (N.D. Ill. Sept. 14, 2001), *aff'd*, 316 F.3d 1348 (Fed. Cir. 2003); *Allergan, Inc. v. Alcon Labs., Inc.*, 200 F. Supp. 2d 1219 (C.D. Cal. 2002), *aff'd*, 324 F.3d 1322 (Fed. Cir. 2003). Yet, in each of those cases, the courts simply deferred to FDA and reviewed the statute in instances where the patented uses were "unapproved." That is, the ANDA applicant would not be seeking approval of the patented use as it was not an approved use for even the innovator product at that time. The instant case, as well as others like it, including the *AstraZeneca* case, give rise to a different problem with FDA's "either/or" policy.

First, to be listed in the Orange Book, the method of use patent must claim at least one approved FDA use that is indicated for in the brand products label. *Applications for FDA Approval to Market a New Drug*, 68 Fed. Reg. at 36,681 ("If an NDA applicant or holder or patent owner intends to submit information on a patent that claims a method of use, the patent must claim a use that is described in the NDA. If we have already approved the NDA, the patent must claim a method of use that is in the labeling of the approved NDA."). This requirement alone makes the *Warner-Lambert* gabapentin cases and *Allergan* case anomalies. *See Warner-Lambert*, 316 F.3d at 1354–55 (concluding that "it is not an act of infringement to submit an ANDA for approval to market a drug for a use when neither the drug nor that use is covered by an existing patent, and the patent at issue is for a use not approved under the NDA"); *Allergan*, 324 F.3d at 1334 (finding that "Allergan is precluded from suing Alcon and B & L under section 271(e)(2) for inducing infringement of the '415 and '741 patents, because Alcon and B & L

are not seeking FDA approval for the uses claimed in the patents and because the uses claimed in the patents are not FDA-approved").

After a section viii statement is filed with FDA, under current FDA practice and policy, FDA compares the proposed generic label to the use code and description of the patented method of use. If FDA determines that the label sufficiently carves out the patented method of use, the section viii statement and label can be approved and FDA does not require patent certification. This approval can occur without notice to the patent holder and/or the innovator pharmaceutical company holding the NDA. This is directly contrary to the language of the statute and the legislative history. *See* 21 U.S.C. §§ 355 (j)(2)(A)(vii), (viii); H.R. REP. NO. 98-957, pt. 1, at 22 (requiring an ANDA applicant not seeking approval for certain patent-protected indications for use to submit a certification addressing each Orange Book-listed patent ***and*** a statement concerning the proposed omitted indication for use.) The result, the generic company obtaining approval and bringing its generic product to market without having given the patentee an opportunity to assess infringement, is also contrary to the policy aims of the Act. Indeed, as discussed above, it disincentives innovator pharmaceutical companies from researching and seeking approval of new indications as the balance of the Act is undermined.

Generic and innovator pharmaceutical companies must resolve any disputes concerning patents in private litigation. Efficient resolution of these disputes occurs when the procedures set forth in 21 U.S.C. § 355 are followed. This is the appropriate

avenue for method of use patents, regardless of whether the use may be carved out of the ANDA-filer's label. Indeed, requiring patent certifications for all patents in the Orange Book, branded and generic companies alike will simply follow the mechanism set forth in the statute and determine infringement and validity issues for method of use patents as is done for compound and formulation patents.[4]

Amici respectfully request that this Court reject FDA's "either/or" policy and require the language of the statute be followed for patent all Orange Book listed patents or, in the alternative, remand to the appellate court for further consideration of this issue. In doing so, the policy aims of Hatch-Waxman will be furthered.

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[4] Contrary to Caraco's assertions, requiring a certification and a section viii statement for each listed Orange Book patent will not result in undue delay for generic entry. Rather, it will allow the innovator pharmaceutical company to assess the generic's proposed carved out indication and assess whether its noninfringement contentions based on that carve out are agreeable. Caraco's argument assumes that an innovator pharmaceutical company will frivolously litigate a patent. Such assumption is inappropriate and should not be accepted by the Court.

CONCLUSION

Given the emerging importance of new uses of old drugs, the counterclaim provision of the Hatch-Waxman Act should be narrowly construed in a way that is consistent with the careful balance the Act provides between branded and generic manufacturers. "Use codes" litigation was simply not envisioned by the Hatch-Waxman Act's framers, nor is there any good reason to permit it. Indeed, opening up the counterclaim provision to allow "use code" litigation has the potential to open a Pandora's box of satellite litigation that will be a waste of resources. The Federal Circuit should be affirmed.

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AMICUS CURIAE BRIEF

No. 10-844

In the Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD. AND SUN PHARMACEUTICAL INDUSTRIES, LTD.,

Petitioners,

v.

NOVO NORDISK A/S AND NOVO NORDISK, INC.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF THE GENERIC PHARMACEUTICAL ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

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BRIEF OF THE GENERIC PHARMACEUTICAL ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

INTEREST OF THE *AMICUS CURIAE*[1]

The Generic Pharmaceutical Association (GPhA) is a nonprofit, voluntary association representing more than 100 manufacturers and distributors of finished generic pharmaceutical products, manufacturers and distributors of bulk active pharmaceutical chemicals, and suppliers of other goods and services to the generic pharmaceutical industry. GPhA's members provide American consumers with safe, effective, and affordable generic drugs. Their products account for nearly 75% of all prescriptions dispensed in the United States, and they save consumers more than $120 billion each year.

GPhA's core mission is to improve the lives of consumers by providing timely access to affordable pharmaceuticals. The decision below undermines that goal by enabling brand-name drug manufacturers to block generic drug market entry through the submission of erroneous patent information to

[1] No counsel for a party wrote this brief, in whole or in part, and no counsel for a party or party made a monetary contribution intended to fund the preparation or submission of this brief. No person or entity other than *amicus curiae* or its counsel made a monetary contribution to this brief's preparation or submission. Petitioners and respondents have consented to the filing; their written consents have been submitted to the Clerk.

the Food and Drug Administration (FDA). Indeed, the decision below eviscerates one of the core mechanisms provided by Congress to generic drug manufacturers, skewing the carefully calibrated statutory scheme heavily in favor of brand-name manufacturers and imposing staggering unintended costs on consumers. The decision also severely disrupts the existing drug approval system by converting the FDA's patent listing process into a conduit for misinformation.

GPhA respectfully submits this *amicus curiae* brief to highlight those adverse ramifications of the court of appeals' decision. Because the many benefits of generic drug availability would be substantially diminished if the Federal Circuit's decision is not reversed, GPhA's members have a significant interest in this case.

STATEMENT

1. Congress passed the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act), Pub. L. No. 98-417, 98 Stat. 1585, with the primary objective of "mak[ing] available more low cost generic drugs." H.R. Rep. No. 98-857, pt. 1, at 14 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2647. The Act furthers that objective through two principal mechanisms that allow generic versions of brand-name drugs to be "marketed more cheaply and quickly." *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661, 676 (1990).

First, the Act permits a generic manufacturer to forgo the filing of a full-fledged new drug application

(NDA), see 21 U.S.C. § 355(b), and instead to file an abbreviated new drug application (ANDA), see 21 U.S.C. § 355(j). If the generic applicant's ANDA demonstrates that the generic version is bioequivalent to the brand-name drug, the ANDA may rely on the clinical safety and efficacy data submitted by the brand-name manufacturer with its NDA, thus eliminating costly and time-consuming duplication of clinical studies. See *Eli Lilly*, 496 U.S. at 676; *Merck KGaA* v. *Integra Lifesciences I, Ltd.*, 545 U.S. 193, 196 n.1 (2005) (citing 21 U.S.C. § 355(j)(2)(A)(ii), (iv), and (8)(B)).

Second, the Act seeks to facilitate the resolution of disputes over the validity and scope of patents that the brand-name manufacturer claims protect its product. The Act does so by requiring an NDA applicant to

> file with the [NDA] the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the [NDA] or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.

21 U.S.C. § 355(b)(1). FDA regulations in turn specify a more exhaustive list of "patent information" that must be submitted with the NDA. See 21 C.F.R. § 314.53(c)(1)-(2). This case concerns "method-of use patents," *i.e.*, patents that "claim[] a method of

using" the drug.[2] For such patents, FDA regulations require brand-name manufacturers to include in the patent information submitted with an NDA a "description of the patented method of use." 21 C.F.R. § 314.53(c)(2)(ii)(P)(3). This description is known as a "use-code narrative" or "use code."

Once an NDA is approved, the drug and its associated patent information are listed in the FDA publication, *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the Orange Book. See 21 U.S.C. § 355(j)(7)(A)(i)(I) and (ii). ANDA applicants rely on the patent information in the Orange Book in deciding whether to seek FDA approval for a generic version of a brand-name drug and, if so, for which uses and by which administrative mechanism. The FDA likewise relies on the Orange Book when determining the scope of the brand-name manufacturer's patent; FDA does not have the authority or expertise to evaluate substantively the accuracy of patent information submitted with an NDA.

2. An ANDA must contain a response to each patent listed in the Orange Book for the brand-name drug that the ANDA references. See 21 U.S.C. § 355(j)(2)(A)(vii). With respect to each such patent,

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[2] Method-of-use patents apply not to the drug itself but to the manner in which the FDA has authorized the drug to be used. For example, a brand-name manufacturer may hold a patent on using Drug X, in combination with Drugs Y and Z, to treat a particular disease. However, other approved methods of using the drug—such as combining that same Drug X with Drugs A and B to treat a different disease—may not be patented.

the applicant generally must certify that: (I) the required patent information has not been filed with the FDA; (II) the patent has expired; (III) the patent will expire on a specified date; or (IV) the patent is invalid and/or will not be infringed by the manufacture, use, or sale of the generic drug for which the ANDA is submitted. 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV).

The lattermost option is known as a "paragraph IV" certification. An ANDA applicant filing a paragraph IV certification must provide the brand-name manufacturer with a detailed basis for its belief that the patent is invalid and/or not infringed. See 21 U.S.C. § 355(j)(2)(B)(i). The submission of a paragraph IV certification is, by statute, a technical act of patent infringement. 35 U.S.C. § 271(e)(2)(A). If the brand-name manufacturer files a patent infringement suit within 45 days after receiving notice of the paragraph IV certification, the FDA's approval of the ANDA is automatically stayed for 30 months, unless a court determines before that time that the patent is invalid or would not be infringed by the marketing of the generic drug. 21 U.S.C. § 355(j)(5)(B)(iii). The court entertaining the infringement lawsuit has discretion to extend the stay beyond 30 months. *Ibid.*

3. In some instances, the patent on the listed drug itself will have expired, but a brand-name manufacturer will possess an unexpired method-of-use patent covering a particular approved use for the drug. If such a patent claims at least one—but fewer

than all—approved uses, an ANDA applicant may seek approval solely for the unpatented uses.

In such cases, rather than submitting a paragraph IV certification, the ANDA applicant may submit to the FDA a statement that the relevant patent "does not claim a use for which the applicant is seeking approval." 21 U.S.C. § 355(j)(2)(A)(viii). That type of submission is known as a "section viii" statement. The ANDA applicant making a section viii statement must also remove or "carve out" any mention of the patented method of use from its proposed labeling for the generic drug. 21 C.F.R. § 314.92(a)(1). The FDA will approve the section viii statement only if there is no overlap between the proposed carve-out labeling and the use code(s) listed by the brand-name manufacturer in the Orange Book. Pet. App. 6a.

Although both a paragraph IV certification and a section viii statement may permit an ANDA applicant to obtain FDA approval before expiration of a patent listed in the Orange Book, the two options have very different implications for the timing of such approval and thus for the entry of generic drugs into the marketplace. A paragraph IV certification will significantly delay FDA approval in many cases, because the brand-name manufacturer can trigger the 30-month automatic stay simply by filing an infringement suit. The filing of a section viii statement, by contrast, does not itself delay approval of an ANDA, see 21 U.S.C. § 355(j)(5)(B)(i)-(iii), because it asserts that the patent as described in the Orange

Book does not even claim to cover the use in question.

4. Brand-name manufacturers have long sought to block or delay generic competition through manipulation of the Hatch-Waxman Act's patent-listing procedures. Because generic drugs are so much less expensive than their brand-name counterparts, generic entry almost immediately results in a large decrease in the brand-name incumbent's sales price and market share. See Cong. Budget Office, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry* 28 (July 1998).[3] A study prepared by the Congressional Budget Office determined that, within a year of entering a market, generic drugs accounted for an average of 44% of prescriptions dispensed through pharmacies. *Ibid.* For seven of the drugs examined in the study, the generic manufacturers' share of the market was 65% or more within two years. *Ibid.*

That swing in market share is typically accompanied by fierce price competition. "For products that attract a large number of generic manufacturers, the average generic price falls to 20% of the branded price and lower." FDA, *Generic Competition and Drug Prices* (Mar. 1, 2010).[4] Those savings redound directly to consumers' (and taxpayers') benefit. A recent study reported that

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[3] Available at http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf.

[4] Available at http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm129385.htm.

generic drugs "saved the nation's health care system more than $824 billion dollars" over the last ten years, with savings of $139.6 billion in 2009 alone. IMS Health & Generic Pharm. Ass'n, *Savings Achieved Through the Use of Generic Pharmaceuticals 2000-2009*, at 1 (July 2010).[5]

Brand-name manufacturers therefore have powerful incentives to delay generic entry for as long as possible. They can accomplish that goal by overstating the scope of their patents or by filing patents of dubious validity or applicability. A generic manufacturer may then file a paragraph IV certification denying the validity of the patent, but the brand-name manufacturer can then obtain an automatic 30-month stay of the generic's FDA approval simply by filing an infringement suit within 45 days. See Stacey L. Dogan & Mark A. Lemley, *Antitrust Law and Regulatory Gaming*, 87 TEX. L. REV. 685, 715 (2009) (noting that brand-name manufacturers have "exploit[ed] the product-approval process" and "convert[ed] it into a tool for suppressing competition").

Recognizing that brand-name manufacturers could effectively frustrate generic competition by listing inaccurate or overbroad patent information in the Orange Book, Congress amended the Act in 2003 to provide a method for generic manufacturers to address such gamesmanship regarding method-of-use patents. Specifically, Congress authorized defen-

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[5] Available at http://www.gphaonline.org/sites/default/files/GPhA%20Savings%20Study%20Book%20Updated%20Web%20FINAL%20Jul23%2010_0.pdf.

dants in a paragraph IV infringement action (*i.e.*, generic manufacturers) to bring a "counterclaim seeking an order requiring the [patent] holder to correct or delete the patent information submitted by the holder * * * on the ground that the patent does not claim * * * an approved method of using the drug." 21 U.S.C. § 355(j)(5)(C)(ii)(I). The availability of such a counterclaim forms the basis of the dispute here.

5. This case arises from petitioners' application to the FDA for approval to sell a generic version of repaglinide, a diabetes drug manufactured by respondents under the brand name PRANDIN. Petitioners sought approval of generic repaglinide for two uses that respondents concede did not violate their patents on the drug. Nevertheless, respondents sought to block petitioners' application by amending the description of a patent on file with the FDA to claim (erroneously) that the patent in fact covers petitioners' proposed use. As a result, the FDA rejected petitioners' request for approval of labeling that would omit reference to the patented method for using repaglinide, thereby disabling petitioners from arguing that the generic version they sought to distribute would not infringe respondents' patent.

Respondents brought this patent infringement action against petitioners for filing an ANDA for a generic version of repaglinide. Petitioners filed a counterclaim under 21 U.S.C. § 355(j)(5)(C)(ii)(I), seeking an order requiring respondents to correct the description of their patent listed in the Orange Book. The district court entered an order directing respon-

dents to replace their overbroad use code with the previously submitted, correct listing.

A sharply divided panel of the Federal Circuit reversed. The majority held that the Act's counterclaim provision was unavailable to petitioners for two reasons.

First, the majority interpreted the statutory phrase "an approved method of using the drug" as foreclosing the bringing of a counterclaim any time the listed patent claims *any* approved method of using the drug—even if it is not the use for which the generic manufacturer seeks approval. Pet. App. 12a. That is, even if the use code listed in the Orange Book indisputably encompasses unpatented uses, the generic manufacturer cannot counterclaim to challenge that description, so long as the description is broad enough to cover at least one patented use.

Second, the majority construed the term "patent information" in the provision as referring *only* to the patent's number and expiration date. Pet. App. 15a. Under that reading, a generic manufacturer may not file a counterclaim to "correct or delete" the use code information submitted by the NDA applicant to the FDA. The majority interpreted this limitation as further proof that the Act "does not allow generic manufacturers to counterclaim unless the listed patent bears no relation to the listed drug." Pet. App. 14a.

This Court requested the views of the Acting Solicitor General. The Acting Solicitor General

advised this Court that the decision below is incorrect. This Court granted certiorari.

SUMMARY OF ARGUMENT

The question presented is whether a generic drug manufacturer seeking to market an approved drug for *unpatented* uses may file a counterclaim against the brand-name manufacturer in a patent infringement action to require the brand-name manufacturer to correct the inaccurate method-of-use patent information submitted to the FDA. The statute's text, structure, and purpose clearly answer that question in the affirmative. This brief focuses on two serious errors the Federal Circuit committed in concluding otherwise.

A. First, as Judge Gajarsa correctly observed in dissent below, the Federal Circuit's decision "eviscerates" the important section viii process. Pet. App. 62a. Because ANDA applicants will now be unable to challenge overbroad method-of-use patent descriptions via a counterclaim, such descriptions will proliferate in the Orange Book, leading the FDA to reject otherwise proper section viii carve-out statements by generic manufacturers. As a result, generic manufacturers will be forced to proceed by the time-consuming and costly paragraph IV certification process (read: patent infringement litigation), or to withhold their product from the market altogether until the patent expires.

Forcing generic manufacturers to choose either intolerable option is entirely inconsistent with the statutory scheme, given Congress's clear intent to

afford the streamlined section viii process when generic drug approval is sought for non-infringing uses only. The section viii mechanism has been vitally important to the success of many generic drugs, and its unavailability will impose serious, adverse consequences on generic manufacturers and the American public alike.

B. Second, the Federal Circuit's decision renders meaningless the statutory language authorizing generic manufacturers to request that brand-name manufacturers "correct or delete" improper patent information submitted to the FDA. The decision below also disregards other language in the Act and the FDA's reasonable regulations. Furthermore, it runs contrary to the purposes for which patent information is maintained in the Orange Book. As explained below, these failures will further encourage brand-name manufacturers to submit overbroad patent descriptions to the FDA, fundamentally undermining the effectiveness of the patent-listing process.

ARGUMENT

The court of appeals' erroneous decision provides brand-name manufacturers with a roadmap for blocking FDA approval of generic drugs that would not infringe any patent held by the brand-name manufacturer. If left standing, it will lead to severe, unintended consequences for generic manufacturers, the FDA's regulatory regime, and American consumers.

A. The Decision Below Eviscerates The Important Section viii Statement Process

The Act's counterclaim provision is the backstop that ensures proper functioning of the section viii process. By eliminating the availability of a counterclaim in cases such as this, the decision below removes a crucial check on the submission of misleadingly broad patent use code descriptions by brand-name manufacturers, and renders the important section viii mechanism for generic drug approval a "dead letter." Pet. App. 62a. The decision thus disrupts the entire regulatory scheme.

1. As explained above, the Federal Circuit held that a defendant in a paragraph IV infringement lawsuit may assert a counterclaim *only* if the patent at issue does not claim *any* approved method of using the drug. That rule forecloses the bringing of a counterclaim if the manufacturer of a brand-name drug holds a patent that covers at least one (but fewer than all) of the approved methods for using that drug, that manufacturer files an admittedly overbroad use code description with the FDA, and the generic manufacturer seeks approval to market a generic version of the drug for only unpatented uses.

The unavailability of a counterclaim in such circumstances will further motivate brand-name manufacturers to submit overbroad use codes to frustrate generic competition. The proliferation of overbroad use codes in the Orange Book creates serious problems for generic manufacturers who would otherwise seek FDA approval via the more stream-

lined section viii process. Because an overbroad use code will erroneously claim both patented *and* unpatented uses of the relevant drug, a generic manufacturer will be unable to "carve out" the patented use, and the FDA will not accept the generic manufacturer's section viii statement.

2. If the section viii carve-out process is unavailable, ANDA applicants seeking to bring generic drugs to market for unpatented uses face limited choices. The FDA can do little to stem the problem of overbroad use codes, because it does not substantively review or analyze the patent information submitted to it, and will not correct information in the Orange Book unless the brand-name manufacturer withdraws or amends its listing. See 21 C.F.R. § 314.53(f). The FDA's involvement in the patent-listing process is, by design, "purely ministerial." *Teva Pharm., USA, Inc.* v. *Leavitt*, 548 F.3d 103, 106 (D.C. Cir. 2008). As the agency has explained, there is no "statutory basis for a substantive agency review of patents," and the FDA "lack[s] expertise in patent matters" in any event. 68 Fed. Reg. 36,683 (2003).

Nor is the paragraph IV certification process an adequate substitute for submitting a section viii statement. Because filing a paragraph IV certification is a technical act of patent infringement, the ANDA applicant is subject to immediate suit by the brand-name manufacturer. Such a lawsuit imposes significant burdens not associated with the filing of a section viii carve-out statement.

First, in defending a paragraph IV infringement suit, the ANDA applicant must clear a far more onerous hurdle than the showing required under section viii. The ANDA applicant-turned-defendant must prove in court that the brand-name manufacturer's patent is invalid and/or will not be infringed by the manufacture, use, or sale of the generic. See 21 U.S.C. § 355(j)(2)(A)(vii)(IV). Where (as here) the brand-name manufacturer has overstated what the patent actually covers, however, the unavailability of a counterclaim to correct the improper patent description may well make it *impossible* for the generic manufacturer to prove non-infringement. That is because the generic manufacturer will be forced to market the drug with the same label as its brand-name counterpart, which is *by definition* infringing with respect to the patented use. See Pet. App. 50a (Dyk, J., dissenting) ("Novo's adoption of a broad use code for PRANDIN likely prevents Caraco from being able to disprove infringement in the paragraph IV lawsuit, because Caraco is now compelled to include information regarding the patented combination therapy in its label."); Pet. App. 63a (Gajarsa, J., dissenting from denial of rehearing en banc) ("Caraco also cannot disprove infringement in the infringement lawsuit because the FDA requires it to use Novo's original label, which includes information regarding the patented combination therapy.").

In such circumstances, the generic manufacturer's only recourse will be to attempt to prove that the brand-name company's entire method-of-use

patent is invalid. Alternatively, the generic manufacturer may choose to abandon its approval efforts altogether and wait until the very last relevant method-of-use patent held by the brand-name manufacturer expires. Obviously, neither option is attractive to an applicant seeking agency approval for uses that in no way infringe the patent.

It is this added imposition of being required to prove *invalidity* of the entire patent—as opposed to *non-infringement* of a particular use—that the panel majority failed to appreciate when it concluded that its interpretation of the Act "facilitates efficient resolution of disputes concerning potential overlapping of protected and unprotected uses." Pet. App. 14a. Where, as here, a generic manufacturer seeks approval of a drug for unpatented uses only, the lower court's decision does not "strike a balance of the pioneering and generic manufacturers' interests," *ibid.*; rather, it awards a windfall to strategic brand-name manufacturers that have (even intentionally) submitted overbroad patent descriptions to block generic competition.[6]

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[6] While acknowledging that Novo's broad use code "threatens to impair Caraco's ability to disprove infringement" in paragraph IV litigation, the concurrence below incorrectly attributed that result to the FDA's actions in this particular case. Pet. App. 20a; Pet. App. 47a-48a. But the problem is *not* limited to situations in which the FDA initiates a request for a labeling change. When a brand-name manufacturer submits an overbroad use code in the first instance, it is equally foreseeable that the generic manufacturer will be unfairly forced to proceed via a paragraph IV certification and make a showing of patent invalidity.

Moreover, even if a generic manufacturer is ultimately successful in a paragraph IV infringement suit, it will have suffered significant unwarranted delay in market entry because of the automatic 30-month stay. See 21 U.S.C. § 355(j)(5)(B)(iii). Such delay imposes enormous costs on consumers: One commentator has estimated that, for a set of 21 widely prescribed prescription drugs, a mere one-year delay in the entry of generic competition "represents, under conservative assumptions, a transfer from consumers to producers of about $14 billion." C. Scott Hemphill, *An Aggregate Approach to Antitrust: Using New Data and Rulemaking to Preserve Drug Competition*, 109 COLUM. L. REV. 629, 650 (2009). Add to that the additional costs and uncertainty inherent in *all* federal litigation—particularly complex patent litigation. Cf. *Teva Pharm., USA, Inc.* v. *Sebelius*, 595 F.3d 1303, 1305 (D.C. Cir. 2010) (filing paragraph IV certification introduces "hazard of sparking costly litigation").

The section viii process, by contrast, avoids litigation altogether. Indeed, the whole point of a section viii statement is to permit a generic manufacturer to sell a drug *immediately* when it is approved for only an unpatented use. See, *e.g.*, *Purepac Pharm.* v. *Thompson*, 238 F. Supp. 2d 191, 195 (D.D.C. 2002) (immediate approval offered by section viii makes it "an attractive route for generic manufacturers"), aff'd, 354 F.3d 877 (D.C. Cir. 2004). The prospect that the generic manufacturer *may* ultimately prevail in proving invalidity, after long and costly litigation, is cold comfort.

3. Evisceration of the section viii process is particularly inappropriate, given the mechanism's crucial function in the larger regulatory scheme. Limiting the availability of the process is inconsistent with the statute, the legislative history, and the case law.

First, the section viii carve-out process derives from clear statutory language. Section viii specifically addresses how ANDA applicants should address method-of-use patents, and it explicitly authorizes the ANDA applicant to declare "that the method of use patent does not claim" the use for which approval is sought. 21 U.S.C. § 355(j)(2)(A)(viii). There is no limiting language—in section viii or elsewhere in the statute—requiring more.

Second, the Act's legislative history demonstrates that Congress anticipated that there could be brand-name drugs approved for multiple uses, where only some of those uses were patented, and that there should be no barrier to entry for generic drugs seeking approval for unpatented uses. See Pet. App. 38a. The report accompanying the House version of the Act noted that the Act "permits an ANDA to be approved for less than all of the indications for which the listed drug has been approved." H.R. Rep. No. 98-857, 1984 U.S.C.C.A.N. at 2654; see also *Bristol-Myers Squibb Co.* v. *Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996) (citing this statement as "unusually strong support" for the notion that the Act does not prevent a generic manufacturer from obtaining approval for fewer indications than the FDA has approved for the brand-name manufacturer).

Indeed, the report discusses an example in which a listed drug has been approved for two indications, but only one of those indications is protected by a method-of-use patent. It recognizes that, in such circumstances, "the applicant could seek approval for only the [unpatented] indication." H.R. Rep. No. 98-857, 1984 U.S.C.C.A.N. at 2654; see also *id.* at 2655. By "requir[ing] patent owners to submit information to FDA regarding * * * use patents that cover approved drugs," the Act allows "generic copies of these drugs [to] be approved when the patents expire," which furthers Congress's goal of "mak[ing] available more low cost generic drugs." *Id.* at 2647-2648.

Finally, courts also have recognized the crucial importance of section viii as an available option for qualifying ANDA applicants. For example, in *Purepac Pharmaceuticals*, a brand-name manufacturer had improperly listed in the Orange Book a patent claiming an unapproved use for a drug. When a generic manufacturer submitted a section viii statement seeking approval of that drug for the actual approved use (not covered by patent), the FDA rejected the statement, reasoning that only approved method-of-use patents *should* be included in the Orange Book, and therefore the listed patent *must have* claimed the actual approved use. The FDA insisted that the parties were required to litigate their dispute in a paragraph IV infringement suit.

The district court directed the FDA to accept the ANDA applicant's section viii statement. The court acknowledged that the paragraph IV "mechanism

slows the process of bringing generic drugs to market, thus assuring the brand manufacturer of a continued monopolistic position in the market." 238 F. Supp. 2d at 207. It observed that, "[i]f used in circumstances not intended by Congress, paragraph IV thus could upset the careful balancing of the rights of NDA holders and the interests of generic manufacturers (and the drug-buying public) that lies at the core of the Hatch-Waxman Amendments." *Ibid.* Thus, where there was no evidence of "any convergence between the scope of [the] method of use patent and the use for which the generic manufacturer seeks to market its drug product," to require a paragraph IV certification "would result [in] a substantial windfall to the NDA holder that cannot be squared with congressional intent." *Ibid.* So too here.

4. Last, but certainly not least, the evisceration of section viii will have dire consequences for American consumers. The decision below effectively extends the term of the brand-name manufacturer's expired drug patent. A generic manufacturer obviously may not sell a brand-name drug for patented uses, but the Federal Circuit's rule renders the generic manufacturer unable to sell the drug for *unpatented* uses covered by the overbroad use code. Thus, it must wait until *all* method-of-use patents held by the brand-name manufacturer expire. Again, this delay in generic entry imposes steep costs to drug purchasers.

Indeed, the section viii process has been historically important to the success of many generic

drugs. For example, FDA's approval of generic ramipril, a popular ACE inhibitor drug for treating hypertension, followed section viii statements filed by several ANDA applicants that carved out patented uses relating to reducing the risk of heart attack and heart failure. See Aaron F. Barkoff, *FDA Denies King Pharma's Citizen Petition Concerning Altace, Approves Ramipril ANDAs* (June 25, 2008).[7] The introduction of generic ramipril in mid-2008 immediately diminished the brand-name manufacturer's market share, resulting in large cost savings for consumers. See King Pharmaceuticals Press Release (Feb. 26, 2009) (company's nearly $200 million revenue loss in Q4 2008 as compared to Q4 2007 was "primarily due to the market entry of generic substitutes for" brand-name ramipril).[8] Another major drug for treating high blood pressure, carvedilol, was approved by FDA in 2007, after generic manufacturers were able to carve out patent-protected uses relating to treatment for congestive heart failure. See FDA, *First-Time Generics – September 2007* (Apr. 30, 2009).[9] Before generic approval, the brand-name drug had annual sales of

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[7] Available at http://www.orangebookblog.com/2008/06/fda-denies-king-pharmas-citizen-petition-concerning-altace-approves-ramipril-andas.html.

[8] Available at http://www.sec.gov/Archives/edgar/data/1047699/000095014409001638/g17835exv99w1.htm.

[9] Available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ANDAGenericDrugApprovals/ucm062071.htm.

approximately $1.6 billion. See Glenmark Pharmaceuticals Ltd. Press Release (Sept. 10, 2007).[10] Predictably, the entry of generic competition led to lower prices and corresponding benefits to consumers.

As the United States noted in urging this Court to grant certiorari (U.S. Inv. Br. 19), in FY 2010 alone the FDA approved 11 ANDAs with carve-out labeling. Over the years, the FDA has rejected the overwhelming majority of petitions filed by brand-name manufacturers seeking to block agency approval of proposed section viii carve-out labels. See Kurt R. Karst, *The Itch Is Scratched – FDA Denies XYZAL Carve-Out Petition; Another Precedent Added to the Generic Drug Labeling Carve-Out Citizen Petition Scorecard* (Feb. 24, 2011).[11] Generic drugs approved via the section viii statement process save consumers billions of dollars each year.

The section viii process looks to be even more critical in the near future. A large number of brand-name drug patents are nearing expiration, and generic manufacturers are well positioned to carve out patented uses of those drugs when seeking FDA approval. See Paula Tironi, *Pharmaceutical Pricing: A Review of Proposals to Improve Access and Affordability of Prescription Drugs*, 19 ANNALS

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[10] Available at http://www.glenmarkpharma.com/GLN_NWS/pdf/Release_CarvedilolApproval_september_062007.pdf.

[11] Available at http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2011/02/the-itch-is-scratched-fda-denies-xyzal-carve-out-petition-another-precedent-added-to-the-generic-dru.html.

HEALTH L. 311, 338 (2010) ("By 2016, pharmaceutical companies are expected to lose $140 billion in annual sales due to patent expiration and the entry of generics."). As a result, brand-name manufacturers have increasingly turned to filing method-of-use patents in an effort to extend their monopoly power. See Kurt R. Karst, *Analysis Shows Patent Use Codes Have Doubled Since August 2003* (July 8, 2010).[12] Should the decision below stand, brand-name manufacturers will have even stronger incentives—and ready means—to leverage patentable, incremental use improvements into a categorical prohibition on generic competition for the duration of the brand's method-of-use patent. Such manipulative tactics will come at the expense of the development of truly new and different advancements, and American consumers will pay the price.

B. The Decision Below Undermines The Purpose Of NDA Submissions To The Orange Book

The Federal Circuit also erred in holding that the Act's counterclaim provision does not authorize an order compelling the patent holder to revise the use-code narrative listed in the Orange Book. The court's unduly narrow interpretation of the term "patent information" undermines the purposes behind NDA

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[12] Available at http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2010/07/analysis-shows-patent-use-codes-have-doubled-since-august-2003--by-kurt-r-karst-httpwwwhpmcomvattorneycfmrid22.html.

submissions to the FDA, and further frustrates the regulatory scheme.

1. For starters, the Federal Circuit's construction renders superfluous the statutory language authorizing "correct[ion]" of "patent information" as a remedy for inclusion of an improper use code. Although "patent information" is not explicitly defined in the Act, FDA regulations spell out a detailed list of "patent information"—including a use-code narrative—that must be submitted with an NDA. See 21 C.F.R. § 314.53(c)(2)(ii)(P)(3). Those regulations were promulgated mere months before Congress passed the amendments that added the counterclaim provision, and they provide the context for the Act's use of the term. See Pet. App. 16a; Pet. App. 33a-38a (Dyk, J., dissenting).

Nevertheless, the court of appeals held that "patent information" means only "the patent number and the expiration date" submitted by the NDA applicant. Pet. App. 15a. Thus, according to the court, a counterclaim may *not* be brought to remedy an improper use-code narrative. That holding, combined with the court's conclusion that a counterclaim is unavailable whenever the patent claims at least one approved use, means that a defendant in paragraph IV litigation may file a counterclaim *only* when the patent submitted by the NDA applicant claims neither the relevant drug nor any approved use for that drug. In such circumstances, however, the patent should not have been listed in the Orange

Book in the first place, and the proper remedy would be to "delete" it, not "correct" it.[13]

Accordingly, the Federal Circuit's decision does not sanction "correct[ing]" patent information that misrepresents the scope of the patent. Indeed, under the court's construction, there are *no* circumstances in which "correct[ion]" of "patent information" will ever be required. The court's interpretation, therefore, does not give meaning to the full statutory provision, and should be rejected. See, *e.g.*, *Reiter* v. *Sonotone Corp.*, 442 U.S. 330, 339 (1979) ("In construing a statute we are obliged to give effect, if possible, to every word Congress used."); see also *ibid.* ("Canons of construction ordinarily suggest that terms connected by a disjunctive be given separate meanings").

Furthermore, although it is generally agreed that Congress enacted the counterclaim provision in part to respond to the Federal Circuit's decision in *Mylan Pharm., Inc.* v. *Thompson*, 268 F.3d 1323 (2001), see Pet. App. 13a, that case cannot dictate the full scope of the statutory provision. See Pet. App. 32a (Dyk, J., dissenting) ("viewing the overruling of *Mylan* as limited to complete delisting would be inconsistent with the explicit statutory language"). Courts are obligated to give meaning to the actual words used

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[13] *Mylan* itself suggests that deletion is the proper remedy in such a case. See, *e.g.*, *Mylan Pharm., Inc.* v. *Thompson*, 268 F.3d 1323, 1330 (Fed. Cir. 2001) ("Mylan and the FDA concede that there is no cause of action to *delist* a patent from the Orange Book.") (emphasis added).

by Congress, even when it legislates more broadly than the originating concern. "[T]he fact that a statute can be applied in situations not expressly anticipated by Congress does not demonstrate ambiguity. It demonstrates breadth." *Penn. Dep't of Corr.* v. *Yeskey*, 524 U.S. 206, 212 (1998) (internal quotation marks omitted) (quoting *Sedima, S.P.R.L.* v. *Imrex Co.*, 473 U.S. 479, 499 (1985)). This Court should respect Congress's actual response to *Mylan* and give effect to the statute's unambiguous text.

2. By authorizing a remedy to "correct or delete" erroneous "patent information," the Act presumes that patent information listed in the Orange Book *should be* correct. If that statutorily prescribed remedy is to have any force at all, it *must* dictate that the NDA applicant tailor its use code to correspond to the legitimate scope of the patent, not to whatever use the brand-name manufacturer chooses to claim.

Requiring NDA applicants to submit a use code that accurately reflects the uses covered by the patent is consistent with the common understanding of the verb "to correct." The Act does not define that term, and therefore the Court should construe it in accordance with its ordinary or natural meaning. See *Chapman* v. *United States*, 500 U.S. 453, 461-462 (1991). To "correct" information is to "make or set right" such information or "rectify" its errors. See Webster's New Int'l Dictionary 597 (2d ed. 1957); see also Webster's Third New Int'l Dictionary 511 (1986) (similar); Webster's Ninth New Collegiate Dictionary 293 (1983) (similar). Certainly, "patent information"

describing uses outside of the listed patent's scope contains errors that courts have the authority to order the NDA applicant to "make or set right" or "rectify."

The Federal Circuit effectively held, however, that there is nothing "to correct" in the Orange Book so long as the brand-name manufacturer's use code description encompasses at least one approved method of using the listed drug—regardless of whether it adheres to the actual scope of the patent. Yet one can imagine a variety of circumstances in which there is great potential to mislead by offering deliberately overbroad information. Suppose, for example, that an individual has moved and is trying to avoid bill collectors. Suppose further that his credit-card agreement requires him "to correct" his address upon moving. Potential disclosures include: "123 Maple Street," "Arlington," "Virginia," "United States," or even "planet Earth." Under the court of appeals' reasoning, any one of these responses would suffice. Similar mischief here can be prevented only if the brand-name manufacturer is required to "make or set right" or "rectify" his submission with reference to the proper scope of the patent itself.

Second, permitting ANDA applicants to require the correction of overbroad use codes harmonizes the counterclaim provision with the statutory language governing the NDA application process. Specifically, the Act requires NDA applicants to submit "the patent number and expiration date of any patent which claims * * * a method of using such drug *and with respect to which a claim of patent infringement*

could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. § 355(b)(1) (emphasis added). This last phrase necessarily establishes an accuracy constraint on the language used to describe a patent in the Orange Book. That is, a patent holder could not "reasonably" "assert[]" "a claim of patent infringement" if the patent's method of use was indefinite or overbroad, and thus the patent information submitted to the FDA likewise may not be so. As the dissent below observed, the final phrase in Section 355(b)(1) "contemplates that the scope of the patent must be accurately described and that the patent must be related to the drug or method of use for which the NDA application is submitted." Pet. App. 27a-28a. (Dyk, J., dissenting). See also 21 U.S.C. § 355(c)(2) (same language in requirements for submission of patent information after submission of NDA).

Finally, because the FDA does not substantively evaluate the patent information submitted by the brand-name manufacturer—and because any disputes as to the correctness of that information must be resolved by the courts—it is especially important that there be a readily administrable standard as to what the "correct[ion]" remedy requires. Cf. *Waldemar Link, GmbH & Co.* v. *Osteonics Corp.*, 32 F.3d 556, 560 (Fed. Cir. 1994) ("The patent system as a whole benefits from clear, unambiguous rules."). Such a clear rule can be supplied only by reference to the patent itself. For that reason as well, use-code

narratives should be required to hew closely to the language of the patents.

3. The Federal Circuit's overly restrictive interpretation of the term "patent information" is also wrong because it renders the counterclaim provision unacceptably ministerial, and is inconsistent with the purposes served by the Orange Book.

The patent information submitted with an NDA is not simply received and catalogued by the FDA for posterity. It is relied on by both the agency and the public in understanding the applicability and scope of relevant patent rights, and it is "essential to the operation of the statute." Pet App. 29a. As the FDA has explained, the "claim-by-claim listing of method-of-use patents" is necessary to permit ANDA applicants "to assess whether they are seeking approval for a use claimed in the listed patent," and thus to "determine whether to submit a patent certification or a section viii statement." 68 Fed. Reg. 36,685 (2003); see also *Purepac Pharm.*, 354 F.3d at 880 ("In order to determine what patents cover existing brand-name drugs and hence whether any paragraph IV certifications or section viii statements are needed, applicants look in the 'Orange Book.'"). It is also necessary so that the FDA "can verify that the certification or statement is correct, and that only the appropriate methods of use are included in the proposed labeling for the ANDA." 68 Fed. Reg. 36,685.

In addition, even before an ANDA is submitted, generic drug manufacturers look to the patent

information maintained in the Orange Book in deciding whether to attempt to commercialize particular drugs for particular uses. Inaccuracy in the listed information therefore disrupts ongoing innovation efforts, and imposes significant costs on generic manufacturers in the form of wasted research and development expenses.

The decision below seriously undermines those basic purposes of the Orange Book by providing a remedy only where a patent number or expiration date has been submitted in error with an NDA. But errors of that sort are merely clerical, and the "correct[ion]" of such discrepancies cannot possibly be the purpose behind the litigation remedy explicitly afforded to generic manufacturers by the statute—Congress did not authorize this cause of action to fix mere scrivener's errors.

The Federal Circuit's decision also undermines the regulatory scheme by treating similarly situated NDAs differently. Under that court's reading, an NDA applicant may be required to "delete" the submitted patent information if it does not appropriately relate to the listed *drug*, but may not be required to "delete" it if it does not relate to the patented *method of use*. As the dissent below observed, however, "[t]here is no basis in the statutory language or statutory purpose for distinguishing between drug information and method of use information. Either both must be 'patent information,' or neither must be patent information." Pet. App. 33a (Dyk, J., dissenting). Clearly, "all Orange Book information is 'patent information.'" *Ibid.*

Similarly, an NDA applicant could be required to "delete" patent information if the use code claims *one* unpatented use, whereas that same applicant would not be required to "delete" patent information if that same unpatented use were listed *in combination with* at least one patented use. This difference in treatment is illogical—in either case, the applicant has submitted inaccurate information. Yet only in the latter case may the brand-name manufacturer manipulate the system to block non-infringing uses by a generic competitor.

4. The Federal Circuit's misguided construction of the counterclaim provision will only further encourage brand-name manufacturers to submit overbroad patent descriptions to the FDA. So long as a brand-name manufacturer has a patent covering at least one approved method of using a drug, the manufacturer can "follow [respondents'] lead and draft exceedingly broad use codes" that will prevent all generic competitors from carving out unpatented uses for the drug. Pet. App. 62a. Secure in the knowledge that overbroad descriptions will not be rejected by the FDA and cannot be challenged in court, brand-name manufacturers can be expected to submit ever-broader patent descriptions.

That prediction is not idiosyncratic. A recent report directed at investors in the brand-name drug industry greeted the decision below with great enthusiasm and predicted that brand-name manufacturers will deliberately and successfully pursue this strategy to extend their lucrative monopolies on certain drugs. See Morgan Stanley Research

Europe, *Pharmaceuticals: Potential Selective Upside for Industry post Prandin Ruling* 2 (Sept. 1, 2010) ("We anticipate that several companies will extract significant [earnings per share] and [net present value] upside from utilization of PUC (Patent Use Code) narrative strategies."); see also *ibid.* ("[W]e anticipate increasing listing of 'use' patents in the Orange Book as the [brand-name] industry seeks to maximize any commercial gains.").[14] In practical terms, such "upside" for brand-name manufacturers is pure "downside" for consumers.

The implications of the lower court's decision will impair the FDA's regulatory function. As the FDA has explained, "[a] fundamental assumption of the Hatch-Waxman [Act] is that the courts are the appropriate mechanism for the resolution of disputes about the scope and validity of patents." 68 Fed. Reg. 36,683 (2003). But the panel majority's conclusion means that there will be no judicial forum available to resolve disputes over the scope of a brand-name manufacturer's use-code narrative. By thus removing the only effective check on the submission of misleading patent descriptions for publication in the Orange Book, the decision below renders the FDA's patent listing process a conduit for misinformation.

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[14] Available at http://www.fdalawblog.net/files/morgan-stanley-rpt---puc-decision.pdf.

Before the Hatch-Waxman Act's passage, generic drugs accounted for about 12% of all prescriptions filled in the United States. See FDA, *Greater Access to Generic Drugs* (Jan. 2006).[15] Today, by contrast, roughly 75% of all U.S. prescriptions are filled with generic drugs, and domestic sales of generic drugs average more than $50 billion per year. See Jonathan D. Rockoff, *Prescription-Drug Sales Rise 5.1%*, Wall St. J., Apr. 2, 2010; Generic Pharm. Ass'n, *Facts at a Glance*.[16] The successful proliferation of generic drugs—and the massive savings that consumers enjoy as a result—is due in no small part to Congress's enactment and the courts' faithful enforcement of the Act's provisions. The Federal Circuit's decision erects a serious roadblock to maintaining or furthering these savings. This Court should restore the path for generic manufacturers to deliver safe, effective, and affordable drugs to American consumers.

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[15] Available at http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143545.htm.

[16] Available at http://www.gphaonline.org/about-gpha/about-generics/facts.

CONCLUSION

The judgment of the Federal Circuit should be reversed.

Respectfully submitted.

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AMICUS CURIAE BRIEF

No. 10–844

In the Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD., and SUN PHARMACEUTICAL INDUSTRIES, LTD.,

Petitioners,

v.

NOVO NORDISK A/S and NOVO NORDISK, INC.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF *AMICUS CURIAE* MYLAN PHARMACEUTICALS INC. IN SUPPORT OF PETITIONERS

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STATEMENT OF INTEREST*

Mylan is a manufacturer of generic drugs and frequently files Abbreviated New Drug Applications (ANDAs) under the Hatch-Waxman Act seeking approval of the Food and Drug Administration (FDA) to market drugs for particular uses. Mylan often relies on "section viii" statements that the methods of use it is proposing are not patented. *See* 21 U.S.C. § 355(j)(2)(A)(viii). The FDA, however, will not grant approval to launch if a proposed use falls within the description of a patented method of use that is listed in the FDA's "Orange Book." The accuracy of Orange Book patent information is thus critical.

Regrettably, branded manufacturers often overstate the scope of their patents, and the FDA does not police the accuracy of Orange Book information. In *Mylan Pharmaceuticals, Inc. v. Thompson*, 268 F.3d 1323 (2001), the Federal Circuit held that generic drug manufacturers had no right to sue to correct Orange Book listings. In 2003, however, at the behest of the Federal Trade Commission (FTC) and others, Congress expressly authorized ANDA applicants to file counterclaims to correct or delete erroneous Orange Book patent information. *See* 21 U.S.C. § 355(j)(5)(C)(ii)(I). The availability of such counterclaims serves as a much-needed check on

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* Pursuant to Rule 37.6, Mylan certifies that no counsel for a party authored this brief in whole or in part and that no person or entity, other than *amicus* or its counsel, has made any monetary contribution to the preparation or submission of this brief. The parties have consented to the filing of this brief. A letter acknowledging consent by petitioners accompanies this brief, and respondents have filed a letter with the Clerk of the Court providing blanket consent to the filing of *amicus* briefs.

branded drug manufacturers and deters them from supplying misinformation to the FDA.

In this case, however, the Federal Circuit has read the counterclaim provision extremely narrowly, holding that correctable "patent information" is limited to patent numbers and expiration dates and that counterclaims are available only in cases when no approved uses whatsoever have been patented. The decision effectively eviscerates the counterclaim provision and permits branded manufacturers to block legitimate section viii applications with false Orange Book listings.

Mylan urges the Court to reverse the Federal Circuit's decision because the result, if upheld, will be devastating to the generic drug industry and consumers—and costly to taxpayers as well. Although the counterclaim provision seems obscure at first blush, it is in fact critical to ensuring effective operation of the Hatch-Waxman Act.

SUMMARY OF ARGUMENT

Congress authorized ANDA applicants that have been sued for patent infringement to counterclaim to "correct" Orange Book "patent information" that overstates patent coverage, not just to "delete" listings where none of the approved uses is patented. The majority below incorrectly assumed that Congress merely intended to reverse the outcome on the particular facts of *Mylan v. Thompson*, which involved a lawsuit to "delist" a patent from the Orange Book. In fact, Congress acted not only in response to *Mylan v. Thompson*, but against the backdrop of an FTC study that documented a variety of problems that were delaying generic entry and new regula-

tions adopted by the FDA governing Orange Book patent information. The legislative history of the 2003 amendments confirms that Congress sought a general solution to the problem of incorrect information in Orange Book listings. The statutory language authorizing corrections as well as deletions of incorrect patent information confirms that Congress intended to fill the loophole in the statute, not to create a new loophole as the majority below supposed.

The majority below also erred in holding that correctable "patent information" is limited to patent numbers and expiration dates and excludes information about their substantive scope. The term "patent information" should be read in light of Congress's purpose to have patentees identify which drugs and methods remain patented so that ANDA applicants can avoid infringement. The courts should also defer to the FDA's longstanding construction of "patent information," which covers use code narratives and other patent-related information, not just patent numbers and expiration dates.

The Federal Circuit's artificially narrow construction should also be rejected because it would upset the careful balance of the Hatch-Waxman Act. Not only would it gut the counterclaim provision, but it would vitiate section viii as well. If the decision below stands, brand-name drug manufacturers will continue to abuse the Orange Book listing system with impunity because the FDA does not review the accuracy of those listings. With no agency oversight and no judicial review, branded drug companies can effectively block generic competitors from filing section viii certifications. Instead, generic competitors would have to file "paragraph IV" certifications of

patent invalidity, which inevitably lead to expensive, time-consuming litigation and automatic 30-month injunctions against FDA approval. The result would be to delay generic entry just where Congress sought to expedite it. As in *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990), such an interpretation is implausible in light of the structure and purpose of the amendments and must be rejected.

Finally, the Court should bear in mind the significant practical consequences were it to affirm the Federal Circuit's ruling. Patents on the chemical compositions of many leading drugs have expired, and branded drug companies have responded by seeking additional patents on uses of those drugs. If counterclaims to correct Orange Book patent information are limited as in the decision below, branded drug companies will be able to delay generic competition for nonpatented uses, effectively extending expired patents on the basic compositions and greatly and unnecessarily increasing costs to consumers and taxpayers.

The judgment below should be reversed.

ARGUMENT

A. The 2003 Amendments to the Hatch-Waxman Act Were Not Limited to Changing the Result on the Particular Facts of *Mylan v. Thompson*

Congress's 2003 amendments to the Hatch-Waxman Act authorized ANDA applicants to assert counterclaims to "correct or delete the patent information submitted by the holder ... on the ground that the patent does not claim ... an approved method of

using the drug." 21 U.S.C. § 355(j)(5)(C)(ii)(I)(bb). Naturally read, the statute authorizes relief when one or more of the approved uses is not claimed in a patent, despite its inclusion in the Orange Book. The Federal Circuit, however, has read the statute to apply only when *none* of the approved uses is patented. Although the latter reading may be linguistically possible, it is strained and makes no sense when the language is read in context and in light of the underlying object and policy of the statute.

The majority below assumed that Congress merely intended to reverse the result on the particular facts of *Mylan v. Thompson*. Pet. App. 13a, 21a. But while *Mylan v. Thompson* was a notorious example of the problem of branded drug manufacturers overstating patent scope, the 2003 amendments were not limited to that fact scenario or to the particular remedy sought in that case. Congress adopted a more general solution to a broader problem.

In *Mylan v. Thompson*, Mylan filed an ANDA to sell a generic version of the anxiety drug buspirone. Just as Bristol-Myers's patent on buspirone itself expired, Bristol-Myers obtained a new patent on a method of ameliorating anxiety using a metabolite of buspirone. Mylan then filed a section viii statement that the new patent did not claim use of buspirone itself to treat anxiety. The FDA, however, suspended approval of Mylan's ANDA based on Bristol-Myers's assertion that the new patent did cover a method of using buspirone itself. 268 F.3d at 1327–28.

At the time (2001), the FDA allowed ANDA applicants a limited means to dispute the accuracy of patent information listed in the Orange Book. A party could write the FDA to question the accuracy

of the patent information submitted, and the FDA would request that the branded manufacturer confirm the information. By regulation, however, the FDA would not change the patent information in the Orange Book unless the branded manufacturer withdrew or amended its patent information in response to FDA's request. In that case, an ANDA applicant had to provide certifications despite its disagreement with the listing. *Id.* at 1327.

Mylan wrote to the FDA to challenge Bristol-Myers's Orange Book listing on grounds that the new patent was limited to use of a metabolite of buspirone. The FDA sought clarification from Bristol-Myers, which responded that the new patent also covered a method of using buspirone itself. *Id.* at 1328. The FDA accepted Bristol-Myers's word, and the patent remained listed in the Orange Book. *Id.* With no administrative remedy, Mylan sued to force Bristol-Myers to delete the erroneous listing and to require the FDA grant approval of the ANDA. *Id.*

Although the district court granted a preliminary injunction, the Federal Circuit reversed, holding that the Hatch-Waxman Act did not authorize a private cause of action for delisting. *Id.* at 1332. According to the Federal Circuit, Mylan's claim was "analogous to those barred in the long line of cases precluding private rights of action" under the statute. *Id.* Orange Book listings were effectively uncorrectable.

Fortunately, the FTC recognized that this result was unacceptable and lobbied to change it. Earlier in 2001, the FTC had begun a study of a variety of dubious strategies that branded drug manufacturers were using to delay generic entry. The study issued in July 2002, about nine months after *Mylan v.*

Thompson. *See* FTC, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION (July 2002), *available at* www.ftc.gov/os/2002/07/genericdrugstudy.pdf. Among other things, the FTC noted the FDA's lack of substantive review of Orange Book listings, called on the FDA to clarify its listing requirements, and encouraged Congress to consider allowing generic applicants to counterclaim to challenge the correctness of Orange Book listings when sued for infringement by branded manufacturers. *Id.* at v; *see also id.* at 44–45 & n.13 (specifically discussing *Mylan v. Thompson*).

In 2003, Congress responded to the FTC study and intervening regulatory work by the FDA by adopting the amendments at issue here. The legislative history makes plain that Congress broadly intended to stop abuses that had allowed branded drug manufacturers to delay legitimate generic competition, not simply to make available the particular delisting remedy sought in *Mylan v. Thompson*.[1]

Co-sponsoring Senator McCain observed that the amendments were broadly designed to "close[] loopholes in the current food and drug laws that allow brand pharmaceutical companies to protect themselves from generic competition by unfairly extending drug patent life, maximizing company profits on the backs of American consumers." 149 CONG. REC. 15,490, 15,513 (Jun. 19, 2003).

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[1] For a summary of the background and legislative history of the 2003 amendments, see generally Natalie M. Derzko, *The Impact of Recent Reforms of the Hatch-Waxman Regime on Orange Book Strategic Behavior and Pharmaceutical Innovation*, 45 IDEA: THE J. OF L. & TECH. 165 (2005). *See also* Pet. App. 85a–92a (discussion in the district court's decision).

Co-sponsoring Senator Schumer similarly emphasized the broad reach of the amendments, noting that "[t]he provisions close loopholes in the law and end the abusive practices in the pharmaceutical industry which have kept lower-priced generics off the market and cost consumers billions of dollars." 149 CONG. REC. 31,121, 31,200 (Nov. 24, 2003). Those abuses were many and varied:

> [H]ere is what has happened over the last several years. ... A lot of blockbuster drugs were on the market. Their patents were about to expire. The drug industry, accustomed to the high rate of return they have had, came to the conclusion that they had to do everything they could, they had to pull out all the stops to extend their monopolies. They came up with wild and crazy schemes to do it, such as patenting the substance the body makes when the drug is ingested; developing computer programs and listing the patents on the drug; and, in one case, absurdly, a new patent was asked for because the color of the bottle was changed.

149 CONG. REC. 15,490, 15,515 (Jun. 19, 2003) (also noting that "the pharmaceutical industry, instead of spending all its time developing new drugs, was developing new patents ... [and] car[ing] more about hiring good lawyers than good chemists, scientists, and doctors").

In later debates, Senator Schumer commented specifically on the counterclaim provision, observing

that "the provisions enforce the patent listing requirements at the FDA by allowing a generic applicant, when it has been sued for patent infringement, to file a counterclaim to have the brand drug company delist the patent *or correct the patent information* in the FDA's Orange Book." 149 CONG. REC. 31,121, 31,200 (Nov. 24, 2003) (emphasis added). Senator Schumer thus made explicit the drafters' intent not only to authorize complete delisting of inaccurate Orange Book entries, as Mylan had sought in *Mylan v. Thompson*, but also to authorize *correction* of inaccurate Orange Book information where that more nuanced remedy was warranted.

The statutory language reflects Congress's intent to give courts flexibility to correct incorrect Orange Book information in the way that makes most sense in each case. ANDA applicants may counterclaim to

> *correct or* delete the patent information submitted by the holder ... on the ground that the patent does not claim ... an approved method of using the drug.

21 U.S.C. § 355(j)(5)(C)(ii)(I)(bb) (emphasis added). If Congress had intended to limit counterclaims to extreme cases in which a listed patent is wholly inapplicable, it would have limited the remedy to delisting. Instead, recognizing that branded drug manufacturers could abuse the system in a variety of ways, Congress authorized correction as well as deletion of erroneous patent information. In so doing, it ensured that the counterclaim provision covered cases such as this one in which an Orange Book listing recites both patented and unpatented uses. There is no reason to think that Congress intended to open a new loophole when closing the old one.

B. The Court Should Defer to the FDA's Determination That "Patent Information" Includes Information About Patent Scope, Not Just Patent Numbers and Expiration Dates

As just discussed, Congress authorized counterclaims to ensure that generic drug makers have judicial recourse to correct or delete misinformation about patent coverage that branded drug makers have submitted to the FDA. In holding that correctable "patent information" is limited to patent numbers and expiration dates and excludes uses that the patents purportedly cover, the Federal Circuit has defied both the statutory language and the FDA's longstanding interpretation of "patent information."

The Hatch-Waxman Act requires NDA applicants to list patents claiming a drug or method of use "with respect to which a claim of patent infringement could reasonably be asserted." 21 U.S.C. § 355(b)(1)(G). The statute thus expressly contemplates that the patent holder will describe the scope of the patents and relate them to the drug or method of use for which approval is sought. The resulting Orange Book listings are supposed to notify later ANDA applicants which drugs or methods of use are patented so that those applicants can submit appropriate certifications under 21 U.S.C. § 355(j)(2)(A)(vii) and (viii). "Patent information" must be construed broadly in light of that purpose.

Importantly, when Congress adopted the counterclaim provision in 2003, the FDA had already adopted a regulation (the Patent Listing Rule) that broadly construed the scope of "patent information" required under the Hatch-Waxman Act. Under that

regulation, 21 C.F.R. § 314.53, the FDA required patentees to submit not only patent numbers and expiration dates, but also use code narratives and other patent-related information. The FDA's interpretation deserves deference, as courts "have long recognized that considerable weight should be accorded to an executive department's construction of a statutory scheme it is entrusted to administer[.]" *Chevron U.S.A. Inc. v. Natural Res. Def. Council*, 467 U.S. 837, 844 (1984).

Indeed, Congress was not just constructively aware, but *actually* aware of the FDA's broad reading of "patent information" when it adopted the amendment authorizing counterclaims to correct or delete erroneous "patent information." *See Legislative and Regulatory Responses to the FTC Study on Barriers to Entry in the Pharmaceutical Marketplace: Hearing Before the S. Comm. on the Judiciary*, 108th Cong. 19 (2003) (statement of sponsoring Sen. Schumer: "The bill provides a critical complement to the work the FDA has done in clarifying its regulations on patent listing, but it goes much further."). Such awareness indicates that Congress intended to adopt the FDA's broad view of "patent information."

C. The Federal Circuit's Decision Is Inconsistent with the Careful Balance Struck by the Hatch-Waxman Act

The Hatch-Waxman Act was designed to strike a careful balance between "two competing policy interests: (1) inducing pioneering research and development of new drugs and (2) enabling competitors to bring low-cost, generic copies of those drugs to market." *Caraco Pharm. Labs., Ltd. v. Forest Labs.*,

Inc., 527 F.3d 1278, 1282 (Fed. Cir. 2008) (quotation marks and citation omitted); *see also* Pet. App. 57a–64a (Gajarsa, J., dissenting from denial of rehearing en banc). The Federal Circuit's decision in this case threatens to upset the careful equilibrium established by the Act and its amendments. The decision below renders section viii largely useless and enables branded manufacturers to misuse Orange Book listings to extend *de facto* patent protection and delay legitimate generic competition.

Section viii allows a generic manufacturer to certify that a patent "does not claim a use for which the applicant is seeking approval." 21 U.S.C. § 355(j)(2)(A)(viii). If approved by the FDA, a section viii application permits the generic manufacturer to proceed to market without litigation. There are tradeoffs, however. Even if the section viii applicant is the first to file an ANDA, it is not entitled to 180 days of generic marketing exclusivity. *See* 21 U.S.C. §§ 505(j)(2)(A)(vii)(IV), 505(j)(5)(B)(iv). Furthermore, section viii allows the applicant to market drugs only for particular uses: uses that are FDA-approved and not patented.

As a practical matter, the Federal Circuit's decision vitiates section viii. Patent holders can unilaterally prevent section viii certifications by submitting overly broad use descriptions to the FDA. The FDA does not scrutinize Orange Book listings because it claims to lack expertise on patent issues. *See Purepac Pharm. Co. v. Thompson*, 354 F.3d 877, 885 (D.C. Cir. 2004) (FDA "refuses to determine independently what use a patent covers and instead accepts at face value the use claimed by the patent holder"); 21 C.F.R. § 314.53(f) (FDA "will not change the

patent information in the list" unless the patentee requests). And now the Federal Circuit has held that the courts are powerless to force brand-name manufacturers to acknowledge that their patents cover certain uses but not others.

For example, assume a branded manufacturer's patents on a compound and a method of using it to treat disease 1 have expired, but a patent on using the compound to treat disease 2 remains in force. If the statute worked as Congress intended, a generic drug maker could file a section viii certification and enter the market with a carve-out label limited to treating disease 1. The branded manufacturer, however, can stifle that competition by submitting an overbroad description covering both uses. The FDA will not approve the generic's ANDA because the proposed use falls within the Orange Book description submitted by the patent holder, even though the patent on its face does not cover the use of the drug to treat disease 1. The FDA also will not review the accuracy of the Orange Book description, and the Federal Circuit has now held that the courts are impotent too, even though Congress adopted the counterclaim provision to prevent just this type of chicanery.

To be sure, a generic competitor may still file a "paragraph IV" certification of noninfringement, but that is cold comfort. Even though the generic manufacturer has no desire to promote the patented use of the drug, the statute normally will require it to match the original drug labeling covering both patented and unpatented uses. *See* 21 U.S.C. § 355(j)(2)(A)(v). The patentee will then claim that the generic has induced infringement by selling the

drug with broad labeling that has no carve-out. In most cases, the generic's defenses will be limited to invalidity and inequitable conduct, difficult defenses to establish given the prevailing burdens of proof. Moreover, paragraph IV litigation is expensive, time-consuming, and leads to an automatic 30-month stay of FDA approval under 21 U.S.C. § 355(j)(5)(B)(iii). That expense and delay would not occur if the generic manufacturer could carve out the unpatented use under section viii. Ironically, but inevitably, generic entry would be stalled in the very cases where Congress sought to accelerate it.

This Court has previously considered the careful balance of the Hatch-Waxman amendments in *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990). In that case, the Court addressed whether the safe harbor of 35 U.S.C. § 271(e)(1) extended to use of inventions to obtain marketing approval of medical devices. In ruling that the exemption from infringement should be broadly construed, the Court noted the structure of the Act as a whole and the aim of the Act to "respond to two unintended distortions ... produced by the requirement that certain products must receive premarket regulatory approval." 496 U.S. at 669. On the front end, a patent holder could not reap the benefit of its invention until receiving regulatory approval. *Id.* On the back end, the "combined effect of the patent law and the premarket regulatory approval requirement was to create an effective extension of the patent term" because even after patent protection expired, potential competitors would be delayed until regulatory approval was obtained. *Id.* at 670. The statute "sought to eliminate this distortion from both ends of the patent period," *id.*, thus maintaining the careful balance between

encouraging development of such products and fostering access to less costly alternatives.

This Court concluded that Congress could not have intended the statute to be interpreted in a way that would allow to stand the very distortions the statute was designed to avoid:

> It seems most implausible to us that Congress, being demonstrably aware of ... dual distorting effects of regulatory approval requirements ... that were roughly offsetting ... should choose to address both those distortions only for drug products; and for other products ... should enact provisions which not only leave in place an anticompetitive restriction at the end of the monopoly term but simultaneously expand the monopoly term itself, thereby not only failing to eliminate but positively aggravating distortion of the 17-year patent protection.

Id. at 672–73. Given the structure of the statute and the acknowledged goal of balancing these distortions, the Court held that "[i]t would take strong evidence to persuade us that this is what Congress wrought, and there is no such evidence here." *Id.* at 673.

This case raises the same concerns about disrupting the carefully designed balance of the Hatch-Waxman Act. The Federal Circuit's interpretation effectively allows branded manufacturers to extend patent protection through incorrect Orange Book listings because section viii carve-outs become impossible. Viewing the structure of the Hatch-Waxman

Act and amendments as a whole, the idea that Congress intended such result is, as in *Eli Lilly*, "implausible."

D. Affirming the Federal Circuit's Decision Would Have Terrible Practical Effects

If allowed to stand, the decision below will have terrible consequences. In particular, it will allow brand-name drug manufacturers to abuse use codes with impunity, effectively blocking generic competition and providing unwarranted patent protection for drug uses that are not patented. The inevitable result will be restricted supply and higher prices for critical drugs.

With no FDA oversight and no judicial remedy, nothing will stop branded manufacturers from artificially extending the scope of their patent protection. As one commentator recognized even before the Federal Circuit's decision in this case, "[i]nstead of appropriately assigning the use code, pioneers may be motivated to assign an extremely broad use code to its method of use, thereby optimizing patent protection."[2] If the decision below is affirmed, they will be especially motivated—and unimpeded.

That is especially worrisome because, before this case, section viii certifications were quite common and becoming increasingly important. Many patents on the basic chemical composition of blockbuster

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[2] Julie Dohm, Comment, *Expanding the Scope of the Hatch-Waxman Act's Patent Carve-Out Exception to the Identical Drug Labeling Requirement: Closing the Patent Litigation Loophole*, 156 U. PA. L. REV. 151, 164 (2007).

drugs have expired or soon will. Foreseeing this, branded manufacturers have secured follow-on patents on particular methods of use in an effort to maintain "evergreen" patent protection.[3] Section viii certifications allow entrants to enter the market yet still respect incumbents' limited remaining patent rights. Moreover, section viii applications are especially useful and popular because, unlike paragraph IV certifications, they are not considered technical acts of infringement under 35 U.S.C. § 271(e)(2)(A) and thus do not automatically trigger the 30-month delay of FDA approval under 21 U.S.C. § 355(j)(5)(B)(iii).

As a practical matter, an affirmance of the decision below would severely reduce if not eliminate the availability of section viii applications, and the resulting lengthy delays in generic entry would result in significant, tangible costs to consumers and taxpayers. On average, generic drugs cost 80 to 85% less than brand-name drugs.[4] Thus, where, as here, generic entry is artificially delayed, drug prices will remain artificially high.

Branded drug companies claim they need patent protection as a reward for undertaking research, but that excuse rings hollow where patent protection on the use at issue has expired. In such cases, the

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[3] *See, e.g.*, Rebecca S. Yoshitani & Ellen S. Cooper, *Pharmaceutical Reformulation: The Growth of Life Cycle Management*, 7 HOUS. J. HEALTH L. & POL'Y 379 (2007) (describing patents procured by pharmaceutical companies to extend the length of patent protection on their products).

[4] *See* Somnath Pal, *Directions in Generic Drugs*, 35 U.S. PHARMACIST 8 (Jun. 17, 2010), *available at* http://www.uspharmacist.com/content/s/127/c/21064.

patentee has already received its just reward. Strategic gamesmanship that improperly broadens and extends patent coverage should not be tolerated.

CONCLUSION

The judgment of the Federal Circuit should be reversed.

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AMICUS CURIAE BRIEF

No. 10-844

IN THE

Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD., AND SUN PHARMACEUTICAL INDUSTRIES, LTD.

Petitioners,

v.

NOVO NORDISK A/S AND NOVO NORDISK INC.,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA AS *AMICUS CURIAE* SUPPORTING RESPONDENTS

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INTEREST OF *AMICUS CURIAE*

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is a voluntary, nonprofit association representing the nation's leading research-based pharmaceutical and biotechnology companies.[1] *See* PhRMA, "About PhRMA," *available at* http://www.phrma.org/about/about-phrma; PhRMA, "PhRMA Member Companies," *available at* http://www.phrma.org/about/member-companies. Pharmaceutical and biotechnology companies are the primary source of new drugs and biologics. These new medicines are estimated to account for 40 percent of the increase in human lifespan between 1986 and 2000. *See* Frank R. Lichtenberg, *The Impact of New Drug Launches on Longevity* 21 (Nat'l Bureau of Econ. Research, Working Paper No. 9754, 2003).

Developing new medicines takes years of work and billions of dollars of investment in research and development. PhRMA members make these investments in reliance on a legal regime that protects any resulting intellectual property. A critical component of this legal regime is the right to market new drugs approved by the Food and Drug

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[1] Pursuant to this Court's Rule 37.6, *amicus curiae* affirms that no counsel for any party authored this brief in whole or in part, that no party or counsel for a party made a monetary contribution intended to fund the preparation or submission of this brief, and that no person other than amicus or its counsel made a monetary contribution intended to fund the preparation or submission of this brief. *Amicus curiae* notes that Respondent Novo Nordisk Inc. is a member of PhRMA. The parties have consented in writing to the filing of this brief.

Administration ("FDA") for a defined period without copycat marketing by generic drug companies. This legal protection provides an incentive for innovator companies to invest in research and development of new pharmaceutical products.

PhRMA's members have a strong interest in preserving the carefully crafted regime for FDA approval of drugs. They also have an interest in the predictability and stability of the laws that protect new drugs from premature copying, and in the legal framework designed to permit prompt and orderly resolution of patent disputes. This complex balance should be maintained, particularly in a case where congressional intent is clear.

BACKGROUND

1. Throughout the history of the United States, the federal government has recognized the importance of intellectual property rights as a means of encouraging innovation. The Constitution provides that Congress has power "[t]o promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries." U.S. Const. Art. I, § 8, cl. 8. Congress has exercised that power by enacting the Patent Act, 35 U.S.C. § 1 *et seq.*, which has recently been amended by the Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011).

Patents are especially critical for the development of new pharmaceutical products. Pharmaceutical research is extremely expensive. Creating a new medicine takes, on average, over a billion dollars. *See PAREXEL Biopharmaceutical*

R&D Statistical Sourcebook 2011/2012, at 163 (Mark P. Mathieu ed., 2011); Joseph A. DiMasi and Henry G. Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?," 28 *Managerial and Decision Economics* 469 (2007). The Congressional Budget Office has determined that "pharmaceutical firms invest as much as five times more in research and development, relative to their sales, than the average U.S. manufacturing firm." Congressional Budget Office, Pub. No. 2589, *Research and Development in the Pharmaceutical Industry* 9 (Oct. 2006), *available at* http://www.cbo.gov/ftpdocs/76xx/doc7615/10-02-DrugR-D.pdf; *see also* Nam D. Pham, ndp consulting, *The Impact of Innovation and the Role of Intellectual Property Rights on U.S. Productivity, Competitiveness, Jobs, Wages, and Exports* 13 (April 2010) (pharmaceutical and medicine industry has average annual research and development expenditure per employee that is more than ten times larger than the average among industries studied). In 2010, PhRMA members invested an estimated $49.4 billion in discovering and developing new medicines. Industry-wide, research and development in 2010 was about $68 billion. *See* PhRMA, *2011 Profile: Pharmaceutical Industry*, at 11 (2011), *available at* http://www.phrma.org/sites/default/files/159/phrma_profile_2011_final.pdf

In addition to being extraordinarily expensive, pharmaceutical research involves a high risk of failure. "The attrition rate from stage to stage is unusually high. It is estimated that as many as 10,000 compounds are synthesized for every ten that reach the stage of human testing. Of these ten

compounds, only one eventually reaches the market." Bert Spilker, *Guide to Drug Development: A Comprehensive Review and Assessment* 21 (2009); *see also PAREXEL Biopharmaceutical R&D Statistical Sourcebook 2011/2012*, at 259 (citing failure rate of 81% to 89% for drugs from first-in-man studies to approval). Only a fraction of new drugs are expected to recoup their research and development costs. Henry Grabowski, John Vernon, & Joseph A. DiMasi, "Returns on Research and Development for 1990s New Drug Introductions," 20 *Pharmacoeconomics* supp. 3, 11, at 22-23 (2002).

2. Congress recognized the importance of patents to the field of pharmaceutical research in crafting the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, commonly known as the Hatch-Waxman Act. The Hatch-Waxman Act sought to restore some of the patent term that is lost as a result of FDA's sometimes-lengthy drug approval process. At the same time, Congress sought to prevent patent terms from casting too long a shadow on the efforts of other companies to study and eventually replicate the patented product. The Hatch-Waxman Act "sought to eliminate this distortion from both ends of the patent period." *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 670 (1990).

The Hatch-Waxman Act enables generic "drugs to be marketed more cheaply and quickly" and at the same time maintains incentives for innovation by, among other things, "guard[ing] against infringement of patents relating to pioneer drugs." *Id.* at 676-77. The process Congress created seeks to ensure that disputes between drug pioneers

and generic companies are resolved as early as possible. For example, the Act deems certain filings with FDA to be acts of patent infringement, so that litigation regarding the parties' patent rights can be initiated and resolved promptly. *See id.* at 677-78.

Title I of the Hatch-Waxman Act established a series of steps that ultimately leads, in appropriate cases, to approval of a generic drug.

i. The innovating company files a New Drug Application ("NDA") with FDA. 21 U.S.C. § 355(b)(1). The NDA holder is required to

> file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.

Id.

ii. A generic company wishing to market a generic version of an approved drug may file an Abbreviated New Drug Application ("ANDA"), 21 U.S.C. § 355(j)(1), relying on the fact that the Reference Listed Drug ("RLD"), *i.e.* the drug that the ANDA applicant seeks to copy, was found safe and effective by FDA, *id.* at § 355(j)(2)(A)(i).[2] An ANDA

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[2] A generic company may also submit a section 505(b)(2) application for drug approval under certain circumstances. *See* 21 U.S.C. § 355(b)(2).

must contain one of four certifications as to the patent information identified by the NDA holder stating, in substance, that:

(I) no patent information has been filed,

(II) the patent has expired,

(III) the patent will expire on some stated later date; or

(IV) the patent is invalid or would not be infringed by the generic drug seeking approval.

See 21 U.S.C. § 355(j)(2)(A)(vii).

iii. If a generic company submits a "paragraph IV" certification with its ANDA, it must provide notice to the patent holder and the NDA holder. 21 U.S.C. § 355(j)(2)(B). This notice includes a detailed statement of the factual and legal basis for the generic company's position that the patent is invalid or would not be infringed. 21 U.S.C. § 355(j)(2)(B)(iv).

iv. Pursuant to 21 U.S.C. § 355(j)(2)(A)(viii), if a method-of-use patent is listed with respect to the RLD and the claimed method is not one for which an ANDA applicant is seeking approval, the ANDA applicant may submit a statement that the ANDA does not seek approval for the claimed method. This statement is referred to as a "section viii statement." If an ANDA applicant submits a section viii statement, it is required to carve out those portions of the RLD's labeling that encompass the claimed method. FDA has taken the position that, if a section viii statement is submitted with respect to an approved use claimed by a method-of-use patent, the ANDA applicant is not required to submit a

paragraph IV certification with respect to that patent. *See, e.g.*, FDA, ***Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed***, 68 Fed. Reg. 36676, 36682 (June 18, 2003) (final rule) [hereinafter "Orange Book Rule"].

v. Pursuant to 35 U.S.C. § 271(e)(2), it is an act of patent infringement to submit an ANDA application "for a drug claimed in a patent or the use of which is claimed in a patent . . . if the purpose of such submission is to obtain [FDA approval] to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent or the use of which is claimed in a patent before the expiration of such patent." An ANDA submitted with a paragraph IV certification thus provides a basis for a patent infringement lawsuit. This provision allows for early resolution of patent disputes before a generic drug goes to market. In certain circumstances, commencement of a patent infringement lawsuit pursuant to a paragraph IV certification imposes a 30-month stay on FDA's ability to approve the ANDA. *See* 21 U.S.C. § 355(j)(5).

FDA has issued a series of regulations, forms, and other guidance to implement the complex interaction between intellectual property rights, public health and safety, and market competition established by the Hatch-Waxman regime.

In particular, FDA publishes patent information after approval of an NDA in a compendium titled "Approved Drug Products With

Therapeutic Equivalence Evaluations," popularly known as the "Orange Book." *See* Orange Book Rule, 68 Fed. Reg. at 36676. In addition, FDA has established rules for types of patents that can be listed in the Orange Book. *See* 21 C.F.R. § 314.53 ("Orange Book listing rules").

3. In 2003, Congress amended the Hatch-Waxman regime by, in relevant part, adding a provision that provides a generic drug company in patent litigation with a pioneer company limited rights to assert a counterclaim challenging the Orange Book's listing of patents. *See* 21 U.S.C. § 355(j)(5)(C)(ii)(I), *added by* Medicare Prescription Drug Improvement and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003) ("Hatch-Waxman Amendments"). The counterclaim statute provides:

> If an owner of the patent or the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) on the ground that the patent does not claim either–
>
> > (aa) the drug for which the application was approved; or
> >
> > (bb) an approved method of using the drug.

21 U.S.C. § 355(j)(5)(C)(ii)(I).

FDA's Orange Book listing rules specify, among other things, that "[f]or patents that claim a method of use, the applicant shall submit information only on those patents that claim indications or other conditions of use that are described in the pending or approved application." 21 C.F.R. § 314.53(b)(1). These rules also note that the following information is required:

> (P) Information on each method-of-use patent including the following:
>
> > (1) Whether the patent claims one or more approved methods of using the approved drug product and a description of each approved method of use or indication and related patent claim of the patent being submitted;
> >
> > (2) Identification of the specific section of the approved labeling for the drug product that corresponds to the method of use claimed by the patent submitted; and
> >
> > (3) The description of the patented method of use as required for publication.

21 C.F.R. § 314.53(c)(2)(ii)(P).

The Orange Book listing rules further specify that a patent is submitted for listing in the Orange Book by submitting a form, FDA Form 3542. *See* 21 C.F.R. § 314.53(c)(1); FDA Form 3542, Patent Information Submitted Upon and After Approval of an NDA or Supplement, *available at* http://www.fda.gov/downloads/AboutFDA/Reports

ManualsForms/Forms/UCM048345.pdf [hereinafter "Form 3542"].

Form 3542 includes Question 4.2(b), which asks the applicant to "provide the information on the indication or method of use for the Orange Book 'Use Code' description." The form also provides the following directive for answering Question 4.2(b): "Submit the description of the approved indication or method of use that you propose FDA include as the 'Use Code' in the Orange Book, using no more than 240 total characters including spaces."

"Use codes" are neither required nor defined by the Hatch-Waxman Act; they are a creation of FDA. FDA instructs applicants that the "use code" may track *either* an approved indication *or* method of use. In its "Information and Instructions for Form 3542," FDA provides the following guidance on answering Question 4.2(b):

> The answer to this question will be what FDA uses to create a "use-code" for Orange Book publication. The use code designates a method of use patent that claims the approved indication or use of a drug product. Each approved use claimed by the patent should be separately identified in this section and contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method of use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval. Use a maximum of 240 characters for each "use code."

Form 3542 at 4.

FDA takes the position that its role with respect to patents and Orange Book listings is "ministerial." *See, e.g.*, Orange Book Rule, 68 Fed. Reg. at 36683. It employs the use code system to decide whether to accept an ANDA with carved-out labeling and a section viii statement or to require the ANDA applicant to submit a paragraph IV certification. As noted by FDA, "[u]nless the ANDA applicant can show that it is carving out certain method-of-use labeling, a section viii statement is not a correct submission for the listed patent." *Id.* at 36682.

FDA has stated: "In determining whether an ANDA applicant can 'carve out' the method of use, rather than certify to the listed patent, [FDA] will rely on the description of the approved use provided by the NDA holder or patent owner in the patent declaration and listed in the Orange Book." Orange Book Rule, 68 Fed. Reg. at 36682. Moreover, FDA has explained that "[u]se codes are intended to alert ANDA and 505(b)(2) applicants to the existence of a patent that claims an approved use. They are not meant to substitute for the applicant's review of the patent and the approved labeling." *Id.* at 36683.

SUMMARY OF ARGUMENT

The Hatch-Waxman counterclaim provision does not provide generic drug companies with a means of seeking judicial reformation of the use codes employed by pioneer companies in the Orange Book. Petitioners' argument to the contrary requires rewriting the statutory language, including the requirement that the patent not claim "an approved method of using the drug" and the limitation of relief

to an "order requiring the [NDA] holder to correct or delete the patent information."

1. The plain language of the counterclaim provision precludes Petitioners' interpretation. The provision can be invoked only "on the ground that the patent does not claim either . . . [1] the drug for which the application was approved; or [2] an approved method of using the drug." 21 U.S.C. § 355(j)(5)(C)(ii)(I). Petitioners rely on the second ground for invoking the counterclaim provision, but this ground is inapplicable because Respondents' patent claims "an approved method of using the drug." Moreover, the provision is limited to an order "requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c)." *Id.* "[P]atent information" includes only the patent number and expiration date. It does not include the use code, and thus revision of the use code is not a remedy available under the statute.

2. Because the plain language of the statute is clear, there is no need to consult the legislative history of the counterclaim provision. In any event, the legislative record shows that the provision was intended to provide a means of de-listing from the Orange Book patents that should not have been listed. The provision was a response to the Federal Circuit's ruling in *Mylan Pharmaceuticals, Inc. v. Thompson*, 268 F.3d 1323 (Fed. Cir. 2001). There is no indication that Congress was concerned with overbroad use codes.

3. Petitioners have not established that they are unable to challenge an allegedly overbroad use code. Use codes are a creation of FDA. Accordingly,

Petitioners could have sought a remedy from FDA by, for example, using FDA's Citizen Petition process to ask FDA to engage in notice-and-comment rulemaking to adjust its guidance on use codes or to create a more robust process for interested parties to obtain revisions to use codes. Petitioners could also have requested that FDA change its required labeling for the drug at issue, thereby affecting the choices available to Respondents with respect to the use code. If Petitioners were not satisfied with the FDA's action, they could have brought a judicial challenge under the Administrative Procedure Act. At bottom, Petitioners' complaint is properly directed to FDA; any remedy must involve that agency, not judicial re-writing of use codes.

ARGUMENT

I. The Plain Language Of The Counterclaim Provision Precludes The District Court's Effort To Re-Write The Use Code For Prandin.

This case arises from Petitioner Caraco's effort to market a generic version of PRANDIN® (containing the active ingredient repaglinide) ("Prandin"), a diabetes drug for which Respondent Novo Nordisk Inc. obtained approval pursuant to the filing of an NDA. Respondent Novo Nordisk Inc. submitted U.S. Patent No. 6,677,358 ("the '358 patent), which is assigned to Novo Nordisk A/S, to FDA for publication (*i.e.*, listing) in the Orange Book. As the court of appeals explained, the listing originally included the use code "U-546–use of repaglinide in combination with metformin to lower blood glucose" for this patent. Pet. App. 8a. Respondents later changed the use code for Prandin

to "U-968–A method for improving glycemic control in adults with type 2 diabetes mellitus." *Id.* at 9a. Petitioners view this change, and FDA's subsequent actions based on this change, as improperly hindering their efforts to market a generic version of the drug. In litigation against Respondents, Petitioners invoked the counterclaim provision of the 2003 Amendments to the Hatch-Waxman Act, 21 U.S.C. § 355(j)(5)(C)(ii)(I).

The district court agreed with Petitioners that the counterclaim provision provided a basis for injunctive relief, and ordered Respondents to revert to the original use code. Pet. App. 9a-10a. The Federal Circuit disagreed, finding this to be an improper use of the counterclaim provision. *Id.* at 2a-3a, 12a-17a. The Federal Circuit's decision is correct.

1. When Congress uses unambiguous statutory language, the courts' interpretive task is straightforward. As this Court has stated, "in interpreting a statute a court should always turn first to one, cardinal canon before all others. We have stated time and again that courts must presume that a legislature says in a statute what it means and means in a statute what it says there." *Conn. Nat'l Bank v. Germain*, 503 U.S. 249, 253-54 (1992). "When the words of a statute are unambiguous, then, this first canon is also the last: 'judicial inquiry is complete.'" *Id.* at 254 (quoting *Rubin v. United States*, 449 U.S. 424, 430 (1981)).

By its terms, the counterclaim provision can be invoked only "on the ground that the patent does not claim either . . . [1] the drug for which the application was approved; or [2] an approved method

of using the drug." 21 U.S.C. § 355(j)(5)(C)(ii)(I). Petitioners rely only on the second ground. By its plain terms, however, the second basis for invoking the counterclaim provision is inapplicable, because Respondent Novo Nordisk A/S's patent claims "an approved method of using the drug."

Specifically, the patent at issue claims "[a] method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin." Claim 4, U.S. Patent No. 6,677,358; *see also* Pet. App. 8a. This method—use of repaglinide in combination with metformin—is one of the three FDA-approved uses for Prandin. Pet. App. 7a-8a. The other two approved uses are (a) repaglinide by itself and (b) repaglinide in combination with thiazolidinediones ("TZDs"). *Id.*; *see also* Prandin Approved Labeling (Clinical Trials and Dosage and Administration sections), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020741s038lbl.pdf.

Thus, there is no dispute that Respondents' patent claims "an approved method of using" Prandin. It follows from the plain language of the statute that the counterclaim provision, which addresses patents that have been listed in error, cannot be invoked by Petitioners.

This reading of the statutory language makes good sense and is consonant with FDA regulations. FDA's position is that "[f]or patents that claim a method of use, the applicant shall submit information *only* on those patents that claim indications or other conditions of use that are described in the pending or approved [new drug]

application." 21 C.F.R. § 314.53(b)(1) (emphasis added). Thus, if the patent claims an approved method of use, it should be listed in the Orange Book, so that generic companies are aware of the innovator company's patent and can decide whether and how to proceed and make appropriate certifications under the statute. The corollary to this is that, if a method-of-use patent does not claim an approved method of using a drug, it should not be listed in the Orange Book. The counterclaim provision thus serves a simple yet important purpose: ensuring that those patents that should be listed in the Orange Book are included, and that patents that should not be listed are not included.

In an effort to avoid this straightforward result, Petitioners present a strained interpretation of the statutory language, asserting that, because there are two other approved methods of using repaglinide (*i.e.*, Prandin by itself and Prandin in combination with TZDs), the patent "does not claim . . . an approved method of using the drug." In other words, Petitioners argue that even though Respondent's patent *does* claim an approved use of repaglinide (Prandin in combination with metformin), it somehow simultaneously *does not* claim an approved use, because there exist other approved uses not claimed by the patent. This makes no sense.

Aside from bending logic and normal English usage, Petitioners' interpretation leads to the remarkable conclusion that a patent must claim *all* potential methods for using the drug to be listed in the Orange Book. Under Petitioners' theory, a patent that claimed less than all approved uses

would "not claim . . . an approved method of using the drug," and a counter-claimant would be able to invoke the counterclaim provision. Because the "patent information" defined in the statute does not include the use code, *see infra* pp. 17-19, the only remedy available would be delisting of the patent. There is no reason to think that Congress intended such an unlikely result.

If Congress had meant to establish the regime Petitioners urge, "there were available such infinitely more clear and simple ways of expressing that intent that it is hard to believe the convoluted manner petitioner suggests was employed would have been selected." *Eli Lilly & Co.*, 496 U.S. at 667.

2. Even if the counterclaim provision could be invoked, its plain language precludes the injunctive relief Petitioners seek here. The statute provides that, in the case of a drug listed in error, the counterclaimant may "seek[] an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c)." 21 U.S.C. § 355(j)(5)(C)(ii)(I).

The cross-referenced subsections expressly set forth what Congress meant by "patent information" subject to correction or deletion: "the patent number and the expiration date" of the relevant patent. *Id.* § 355(b)(1); *see also id.* § 355(c)(2) (same information for patents issued after filing of NDA). Subsection (c) addresses situations in which "*the patent information* described in subsection (b)" could not be filed at the same time as the NDA. *Id.* § 355(c)(2) (emphasis added). Language throughout the rest of subsections (b) and (c) reiterates that the patent number and expiration date are "the information"

submitted under these subsections. *See id.* § 355(b)(1), (c)(2).

Moreover, subsection (c) provides that "[u]pon the submission of *patent information* under this subsection, the Secretary shall publish it." *Id.* § 355(c)(2) (emphasis added). This language again makes clear that Congress required that the patent-holder submit the number and expiration date of its patent, and that FDA then publish this information in the Orange Book. *See also id.* § 355(b)(1) ("Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences").

In this case, no court has found that the "patent information," *id.* § 355(b)(1), (c)(2), (j)(5)(C)(ii)(I)—the patent number and expiration date—submitted by Respondents to FDA, and thereafter published by FDA in the Orange Book, is incorrect. Thus, there is no basis to invoke the remedy of "correct[ing] or delet[ing]" the patent information.

Petitioners and their *amici* attempt to inject ambiguity into the counterclaim provision by arguing that confining "patent information" to patent number and expiration date, as defined by the statute, *id.* § 355(b)(1), (c)(2), (j)(5)(C)(ii)(I), would render "correct[ion]" of patent information, *id.* § 355(j)(5)(C)(ii)(I)—as distinct from deletion of patent information—a nullity. Not so. The counterclaim allows for a patent that is listed in the Orange Book under the wrong number to be corrected. And it permits an erroneous expiration date, including one that overstates the duration of the patent, to be corrected. These corrections of

patent information are significant and work to the benefit of generic companies.

The counterclaim provision thus accomplishes important objectives. It prevents the listing in the Orange Book of patents that do not belong there, and it provides for the correction of important information concerning the patents that are listed there. These are material remedies that should not be minimized.

Nothing in the language of the Hatch-Waxman Act or the Hatch-Waxman Amendments supports the view that the "patent information" subject to correction under the counterclaim provision includes use codes. Subsections (b) and (c) do not require submission of use codes or refer to use codes at all. *See id.* § 355(b)(1), (c)(2). Indeed, the Hatch-Waxman Act and Hatch-Waxman Amendments nowhere discuss use codes, let alone define them. There is no textual indication that Congress was concerned with use codes or potential overreaching concerning such entries in the Orange Book. Use codes are thus outside the scope of the counterclaim's correction or deletion remedy.

3. As explained in Part III below, other avenues, apart from the counterclaim provision, were available to Petitioners if they wished to challenge FDA's use code regime. But even if that were not so, it would not justify departure from clear statutory language. As this Court stated recently,

> it is not our task to assess the consequences of each [interpretive] approach and adopt the one that produces the least mischief. Our charge is to give effect to the law Congress

> enacted. . . . If [a certain] effect was unintended, it is a problem for Congress, not one that federal courts can fix.

Lewis v. City of Chicago, 130 S. Ct. 2191, 2200 (2010); *see also Microsoft Corp. v. AT&T Corp.*, 550 U.S. 437, 457 (2007) ("The 'loophole,' in our judgment, is properly left for Congress to consider, and to close if it finds such action warranted.").

II. The Legislative History Confirms That Congress Intended The Counterclaim Provision To Address Circumstances Not Present Here.

Because the plain language of the counterclaim provision precludes Petitioners' request for judicial re-writing of Prandin's use code, there is no occasion to consider the legislative history of the provision. *See Boyle v. United States*, 129 S. Ct. 2237, 2246 (2009) ("Because the statutory language is clear, there is no need to reach petitioner's remaining arguments based on statutory purpose, legislative history, or the rule of lenity."); *Ratzlaf v. United States*, 510 U.S. 135, 147-48 (1994) ("[W]e do not resort to legislative history to cloud a statutory text that is clear."). But even if this Court were to consult the legislative history, it would not support the remedy Petitioners seek.

The legislative record makes clear that the counterclaim provision was intended to provide a means of de-listing from the Orange Book patents that should not have been listed. There are multiple references to the counterclaim provision as authorizing an ANDA applicant to "seek[] removal of a patent listed in the Orange Book," but no

suggestion that the provision had any greater reach. House Conf. Rep. 108-391, at 836 (Nov. 21, 2003), 108th Cong., 1st Sess.; House Debate on Conf. Rep. to accompany H.R. 1, 149 Cong. Rec. H12099 (daily ed. Nov. 20, 2003) (same).

In hearings before the Senate Judiciary Committee on the proposed counterclaim provision, the Chief Counsel of FDA stated that under the Senate bill, "[i]f a suit has been filed, the applicant may assert a counterclaim for an order to require deletion of patent information that the NDA-holder shouldn't have submitted for listing in the Orange Book." Senate Jud. Comm., *Examining the Senate and House Versions of the "Greater Access to Affordable Pharmaceuticals Act": Hearings on Sen. 1 and H.R. 1*, 108th Cong. 1st Sess., S. Hrg. 108-390 (Aug. 1, 2003) (statement of Daniel E. Troy).

This provision responded to the Federal Circuit's decision in *Mylan Pharmaceuticals, Inc. v. Thompson*, 268 F.3d 1323 (Fed. Cir. 2001). In that case, the court of appeals ruled that a generic drug manufacturer does not have a private cause of action to seek de-listing of a patent from the Orange Book. *Id.* at 1325. The generic manufacturer's complaint was that the patent in question "did not claim [the drug] or an approved method of using [the drug]." *Id.* at 1331. This language is mirrored in the statutory counterclaim provision, as is the relief the generic company sought: de-listing from the Orange Book. Congress was well aware of *Mylan* when it enacted the 2003 amendments to the Hatch-Waxman Act. *See, e.g.*, Senate Daily Digest, Debate on Pub. L. No. 108-173, 148 Cong. Rec. S7636-39 (statement of Sen. Wallop) (daily ed. July 31, 2002) (Letter and

policy statement from New York Attorney General Spitzer commenting on S. 812, bill considered prior to eventual amendments, referring several times to the *Mylan* case). The government acknowledges that "*Mylan* was surely significant to Congress" in its consideration of the 2003 amendments. Amicus Br. of United States at 30; *see also* Amicus Br. of the Generic Pharmaceutical Ass'n at 25 ("it is generally agreed that Congress enacted the counterclaim provision in part to respond to the Federal Circuit's decision in *Mylan*").

Notably absent from the legislative record of the counterclaim provision is any congressional concern with use codes. Use codes were not mentioned in connection with the counterclaim provision—or, as far as we can tell, elsewhere in the legislative history of the 2003 amendments. It would be surprising if Congress had expressed a concern with allegedly misleading use codes, because until very shortly before the counterclaim provision was enacted, use codes were drafted *by FDA*. Orange Book Rule, 68 Fed. Reg. at 36683. Overbroad use codes were simply not a concern of Congress's in enacting the counterclaim provision.

In 2002, moreover, Congress considered requiring by statute the submission of additional information beyond the patent number and expiration date. This 2002 bill, which Congress did not ultimately enact, would have amended 21 U.S.C. § 355 by, in relevant part, stating that "[t]he patent information required to be filed" by NDA applicants would include

> (i) the patent number;
> (ii) the expiration date of the patent;

(iii) with respect to each claim of the patent—

(I) whether the patent claims the drug or claims a method of using the drug; and

(II) whether the claim covers—

(aa) a drug substance;

(bb) a drug formulation;

(cc) a drug composition; or

(dd) a method of use;

(iv) *if the patent claims a method of use, the approved use covered by the claim*;

(v) the identity of the owner of the patent (including the identity of any agent of the patent owner); and

(vi) a declaration that the applicant, as of the date of the filing, has provided complete and accurate patent information for all patents described in subparagraph (A).

S. 812, 107th Cong., 2nd Sess., § 3(a)(1) (as sponsored by Sen. Kennedy, July 11, 2002) (emphasis added). But Congress did not enact this provision, and it did not re-define patent information to include "the approved use covered by the claim."

Because Congress declined to enact a definition of "patent information" encompassing a meaning now urged by Petitioners, there is all the more reason to adhere to the plain language of the statute and interpret that phrase as including only the patent number and expiration date. This Court has previously noted instances in which Congress "cut out the very language in the bill that would have authorized" the requested relief. *Doe v. Chao*, 540

U.S. 614, 622 (2004). As the Court explained, "[t]he deletion of [certain language] from the bill is fairly seen . . . as a deliberate elimination of" the covered concept. *Id.* at 623.

The broader statutory context confirms the plain meaning of the statutory language. The Hatch-Waxman Act as a whole was intended to strike a reasonable compromise between the interests of the pioneer drug companies and the generic manufacturers that market copies of the drugs developed by the pioneer companies. As noted in *Mylan Pharmaceuticals, Inc. v. Thompson*, 268 F.3d 1323 (Fed. Cir. 2001):

> These provisions of the Hatch-Waxman Amendments "emerged from Congress' efforts to balance two conflicting policy objectives: to induce name brand pharmaceutical firms to make the investments necessary to research and develop new drug products, while simultaneously enabling competitors to bring cheaper, generic copies of those drugs to market." Thus, Title I of the Act was intended to "make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962." Title II, on the other side of the scale, was intended to benefit pioneer drug manufacturers by "restoring . . . some of the time lost on patent life while the product is awaiting pre-market approval."

Id. at 1326 (internal citations omitted).

The 2003 Amendments promote a balance among all members of the pharmaceutical industry. *See, e.g.*, Senate Daily Digest, Debate on S.1, Prescription Drug and Medicare Improvement Act of 2003, at S8190-91 (June 19, 2003) (statement of Sen. McCain); *id.* at S8191-92 (statement of Sen. Schumer). The 2003 statutory language was carefully crafted to achieve this purpose. Disregarding the plain language of the statute would upset the balance struck by Congress by substituting the policy preferences of certain industry participants for the procedures set forth by statute.

Federal law does not allow "knowingly supplying false use codes," "fraud," Amicus Br. of AARP and U.S. PIRG at 13, 16, or "misrepresenting the scope of [the] patent," Petitioners' Br. at 12. To cite only one example, companies submitting FDA Form 3542 (which calls for the use code) must certify that the information submitted is "accurate and complete," "verify under penalty of perjury that the foregoing is true and correct," and acknowledge a warning that "[a] willfully and knowingly false statement is a criminal offense under 18 U.S.C. [§] 1001." FDA Form 3542. This Court has recognized that

> FDA is empowered to investigate suspected fraud, and citizens may report wrongdoing and petition the agency to take action. In addition to the general criminal proscription on making false statements to the Federal Government, the FDA may respond to fraud by seeking injunctive relief, and civil penalties, . . . and pursuing criminal prosecutions. The FDA thus has

> at its disposal a variety of enforcement options that allow it to make a measured response to suspected fraud upon the Administration.

Buckman Co. v. Pls.' Legal Comm., 531 U.S. 341, 349 (2001) (internal citations and footnotes omitted).

If this Court were to look beyond the plain language of the statute, it should consider that Congress enacted the 2003 counterclaim provision against the backdrop of this Court's 2001 ruling in *Buckman*. In that case, the Court held that private parties may not bring state law tort claims to redress allegedly fraudulent statements made by regulated companies to FDA. As this Court reasoned, "the federal statutory scheme amply empowers the FDA to punish and deter fraud against the Agency, and . . . this authority is used by the Agency to achieve a somewhat delicate balance of statutory objectives. The balance sought by the Agency can be skewed by allowing fraud-on-the-FDA claims under state tort law." *Id.* at 348. The same reasoning applies here, where the Hatch-Waxman regime reflects a careful and somewhat delicate balance of congressional objectives, and where (as described in more detail in the next Part) FDA is amply empowered to adjust its approach to use codes.

In its 2003 amendments to Hatch-Waxman, Congress did not respond to *Buckman* by creating a private right of action to challenge submissions to FDA. Hence, as the law stands, there is no presumption that a private party in Petitioners' position can police, via litigation between two private parties, Orange Book use code statements filed with FDA.

III. Petitioners Are Free To Pursue Other Remedies For Perceived Problems In The Use Code Regime.

Petitioners and their *amici* suggest that, apart from the counterclaim provision, generic manufacturers have no way to challenge use codes on the ground that they are overbroad. *See, e.g.*, Petitioners' Br. at 41-45, Amicus Br. of Mylan Pharmaceuticals Inc. at 16-18. Petitioners have not shown that this is so, and it appears that options for addressing the breadth of use codes are available.[3]

As explained above, use codes are a creature of FDA, not Congress. *See* p. 10, *supra*. FDA Form 3542 instructs pioneer companies to "[s]ubmit the description of the approved indication or method of use" that they propose for the use code. The form, by its terms, provides the option to choose a use code that tracks an approved indication *or* method of use. *See* Form 3542 Question 4.2(b).

FDA has clearly stated that use codes are not strictly limited to a statement of the method of use claimed in the patent. Indeed, in some cases that

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[3] After a bench trial, the district court found the patent-in-suit invalid as obvious and unenforceable due to inequitable conduct. *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 775 F. Supp. 2d 985, 989 (E.D. Mich. 2011). The Federal Circuit has stayed the appeal pending the outcome in this Court. *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, Nos. 2011-1223, 2011 U.S. App. LEXIS 15545 (Fed. Cir. July 27, 2011). If the Federal Circuit affirms on either ground, Petitioner Caraco will have no further need to challenge the Prandin use code narrative.

would be impossible, because of the 240-character limit on use codes:

> Use codes are intended to alert ANDA and 505(b)(2) applicants to the existence of a patent that claims an approved use. They are not meant to substitute for the applicant's review of the patent and the approved labeling. We understand that in some cases 240 characters may not fully describe the use as claimed in the patent.

Orange Book Rule, 68 Fed. Reg. at 36683, 36712.

In 2007, FDA changed its approach to the labeling requirements for oral diabetes treatments. As part of its new approach, FDA "required Novo to replace all separate indications with the following sentence: 'PRANDIN is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.'" Pet. App. 48a n.18 (Dyk, J., dissenting).

Respondents complied with FDA's directive by changing the indication on their Prandin label to conform to FDA's new prescribed language. *See* Respondents' Br. at 49. Respondents also filed papers to have FDA change Prandin's use code in the Orange Book to track the revised indication, *see* Pet. App. 8a-9a, which is one of the approaches contemplated by FDA Form 3542.

It appears that several avenues were available to Petitioners to challenge Prandin's use code.

1. Because FDA's actions are the ultimate source of Petitioners' complaint, FDA is the logical place to turn for potential relief. FDA has a long-

standing Citizen Petition process that allows any person to request virtually any action on the part of FDA, from "issu[ing], amend[ing], or revok[ing] a regulation" to "issu[ing], amend[ing], or revok[ing] an order" to "tak[ing] or refrain[ing] from taking any other form of administrative action." 21 C.F.R. § 10.30.

a. Petitioners could have filed a Citizen Petition asking FDA to engage in notice-and-comment rulemaking that would adjust the applicable regulations and forms (as well as the instructions to the forms) to clarify the policies applicable to situations in which a patent claims some but not all FDA-approved uses. In particular, Petitioners could have asked FDA to adjust its guidance to require the use code to track the method or methods of use claimed in the patent, eliminating the option of having the use code track the approved indication or approved method of use. Petitioners could request that the regulations, forms, and instructions be revised, for example, to require that the NDA applicant submit a use code that either directly quotes the claim language in the patent or paraphrases the claim language with specificity. Relatedly, Petitioners could ask FDA to eliminate from its guidance any statement that permits the use code to be framed in terms of *either* the indication *or* the method of use, and to eliminate the 240-character cap on use code narratives.

b. Petitioners could also have asked FDA to engage in notice-and-comment rulemaking that would create a more robust process for interested parties to obtain revisions to the use codes listed in the Orange Book, as appropriate. FDA allows any

person a limited right to dispute the accuracy or relevance of information submitted under the agency's Orange Book listing rules. *See* 21 C.F.R. § 314.53(f).[4] Caraco is free to pursue a Citizen Petition seeking a different rule, which could complement any revised limitations on use codes by providing a procedure for interested parties (i) to ensure that such limitations are observed and (ii) to request that FDA order any necessary revisions to non-compliant use codes.

c. While changes to the substantive rules and procedures governing use codes would likely be the best means of providing Petitioners with the relief they seek, the same result—having Respondents revert to the original use code for Prandin—could also be achieved if FDA were to withdraw its 2007 directive on the labeling requirements for oral diabetes treatments. If FDA were to change the required labeling so that it distinguished between

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[4] It appears that Caraco sent a letter to the Orange Book staff under this provision, seeking to have the original use code for Prandin reinstated. *See* Caraco Reply Comments, FDA Docket No. FDA-2008-P-0411 (June 16, 2009), at Ex. 2. After Respondents declined to change the use code, Caraco did not follow up with a Citizen Petition asking FDA to order a change to the use code. Nor did it ask FDA to engage in a rulemaking to alter its overall policy under Section 314.53(f) to provide a more robust opportunity for generic companies to seek mandatory changes to use codes.

FDA's public docket reflects that Caraco filed a Citizen Petition regarding repaglinide, but the petition related to Caraco's rights vis-à-vis other generic companies that might file ANDAs, and did not seek a change to Novo's use code. *See* Caraco Citizen Petition, FDA Docket No. FDA-2008-P-0411 (July 14, 2008).

use of repaglinide by itself and use of repaglinide in combination with other therapies, in place of the merged indication the agency currently requires, the result could be that Respondents would not employ the use code to which Petitioners object.

Petitioners have submitted no evidence that they petitioned FDA to provide any of these forms of relief.

2. If FDA did not provide Petitioners with the relief they seek, Petitioners could bring a judicial challenge under the Administrative Procedure Act (APA), 5 U.S.C. § 551 *et seq.* The APA provides that "[a] person suffering legal wrong because of agency action, or adversely affected or aggrieved by agency action within the meaning of a relevant statute, is entitled to judicial review thereof." 5 U.S.C. § 702.

Petitioners had several potential opportunities to seek APA review of FDA's actions, most pertinently when FDA, in the Federal Circuit's words, "disallowed Caraco's section viii statement" on the ground that Caraco's "proposed carve-out label overlapped with the use code U-968 for the '358 patent," Pet. App. 9a; Petitioners also could have filed an APA challenge to FDA's use code regulations or pursued an APA appeal of FDA's denial of any Citizen Petition that Petitioners could have filed. *See generally* 21 C.F.R. § 10.45(d).

The counterclaim provision is not an invitation for courts to enter the business of re-writing use codes. Indeed, we are unaware of any instance, other than the injunction issued by the district court in this case, in which a court has used the counterclaim statute as a basis for ordering revisions to a use code.

The fact that courts have not intervened in this fashion is telling. FDA, which created the use code system, has both the authority and the responsibility to define and regulate the content of use codes.

CONCLUSION

The judgment of the court of appeals should be affirmed.

Respectfully submitted,

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October 2011

AMICUS CURIAE BRIEF

No. 10-844

IN THE

Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD., *et al.*,
Petitioners,

v.

NOVO NORDISK A/S, *et al.*,
Respondents.

On Writ of Certiorari to the United States Court of Appeals For the Federal Circuit

BRIEF OF WASHINGTON LEGAL FOUNDATION AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENTS

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QUESTIONS PRESENTED

Amicus curiae addresses the following issue only:

Whether the counterclaim set forth in 21 U.S.C. § 355(j)(5)(C)(ii) is available to the defendant in a patent infringement action, where the patent that the plaintiff seeks to enforce claims an FDA-approved method of use for the drug for which the defendant seeks marketing approval.

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INTERESTS OF *AMICUS CURIAE*

The Washington Legal Foundation (WLF) is a non-profit public interest law and policy center with supporters in all 50 states.[1] WLF devotes a substantial portion of its resources to defending free-enterprise, individual rights, and a limited and accountable government.

WLF has appeared in numerous federal and state courts in cases raising issues related to health care delivery. *See, e.g., Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653 (2011). In particular, WLF has appeared in cases before this Court and the U.S. Court of Appeals for the Federal Circuit in a number of cases related to the proper resolution of drug patent disputes between "pioneer" drug manufacturers and generic drug manufacturers. *See, e.g., Mylan Pharmaceuticals, Inc. v. Thompson*, 268 F.3d 1323 (Fed. Cir. 2001), *cert. denied*, 537 U.S. 941 (2002); *Allergan, Inc. v. Alcon Laboratories, Inc.*, 324 F.3d 1322 (Fed. Cir.), *cert. denied*, 540 U.S. 1048 (2003).

WLF believes that both pioneer and generic manufacturers play an important role in providing quality health care to the American public. If advances in health care are to continue, it is vital that innovator companies that develop new drugs and medical devices, or new methods of using those products, be afforded

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[1] Pursuant to Supreme Court Rule 37.6, WLF state that no counsel for a party authored this brief in whole or in part; and that no person or entity, other than WLF and its counsel, made a monetary contribution intended to fund the preparation or submission of this brief. All parties have consented to this filing; letters of consent have been lodged with the Court.

periods of patent protection, during which potential competitors are not permitted to market the same product. Patents provide an economic incentive for new product development by ensuring that pharmaceutical companies that gamble the substantial sums necessary for research and development of new therapies will be able to realize a return on their investment when their research and development expenditures bear fruit. On the other hand, once an appropriate period of patent exclusivity has expired, consumers are well served by government policies that encourage other companies to market generic versions of the new drug, thereby ensuring the competition necessary to produce lower prices.

WLF believes that Congress struck an appropriate balance between those competing interests when it adopted the Hatch-Waxman Act.[2] WLF believes it imperative that federal courts refereeing patent disputes between pioneer and generic drug manufacturers strictly apply the procedural rules set forth in the Hatch-Waxman Act. Otherwise, courts will not be giving effect to the careful balance struck by Congress between those two groups of manufacturers. WLF is concerned that Petitioners, by seeking to expand the circumstances under which generic manufacturers are permitted to file legal challenges to the exclusive marketing rights of pioneer manufacturers, are engaged

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[2] The "Hatch-Waxman Act" is the popular name for the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. 98-417, 98 Stat. 1585 (1984), as amended by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003).

in a short-sighted exercise that could, if successful, undermine the long-term interests of the American health care system.

WLF agrees with Novo that Caraco's withdrawal of its Paragraph IV certification deprived the federal courts of jurisdiction to hear Caraco's counterclaim. This brief does not address that issue, however, but rather focuses solely on whether, in light of Caraco's concession that the patent-at-issue claims an approved method of using repaglinide, Caraco is entitled to avail itself of the counterclaim authorized by 21 U.S.C. § 355(j)(5)(C)(ii)(I).

STATEMENT OF THE CASE

Respondents Novo Nordisk A/S and Novo Nordisk, Inc. (collectively, "Novo") market and distribute the drug repaglinide under the brand name PRANDIN. Novo (as the holder of an approved NDA) is the only drug company authorized by the Food and Drug Administration (FDA) to sell repaglinide. PRANDIN is an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. FDA has approved PRANDIN for three uses: (1) repaglinide by itself (*i.e.*, monotherapy); (2) repaglinide in combination with metformin; and (3) repaglinide in combination with thiazolidnediones ("TZDs").

Novo's patent for the chemical composition of repaglinide expired in 2009. However, it holds a method-of-use patent for use of repaglinide in combination with metformin (the " '358 patent") that does not expire until 2018. Accordingly, drug

manufacturers wishing to obtain permission from FDA pursuant to an Abbreviated New Drug Application (ANDA) to market a generic version of repaglinide must demonstrate that they are capable of doing so without infringing the '358 patent.

In 2005, Petitioner Caraco Pharmaceutical Laboratories, Ltd. filed an ANDA with FDA, seeking permission to market repaglinide. The ANDA included a "Paragraph IV" certification with respect to the '358 patent – an assertion that a patent covering the FDA-approved drug (and listed in FDA's "Orange Book") is either invalid or will not be infringed by the sale or use of the generic drug.[3] A provision of the Hatch-Waxman Act (35 U.S.C. § 271(e)(2)) deems the filing of a Paragraph IV certification to constitute an act of patent infringement. Accordingly, Novo responded to Caraco's ANDA by filing a patent infringement suit in June 2005 against Caraco in federal district court in Michigan.

Ordinarily, an ANDA applicant must agree to use the same product labeling previously approved by FDA for use with the brand-name drug to which the proposed generic drug will be compared (known as the "reference listed drug" or "RLD"). If (as here) the FDA-approved labeling includes reference to an approved use that is covered by a method-of-use patent, a generic manufacturer would be unable to avoid infringing the patent if it simply replicated that labeling. The Hatch-Waxman offers a potential remedy for that problem – use of a "Section viii" statement. Section viii, 21 U.S.C. § 355(j)(2)(A)(viii), allows the ANDA applicant to submit

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[3] *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

to FDA a proposed label that carves out the from the RLD labeling the patented method of using the listed drug. FDA will approve the revised labeling, however, only if it determines that the drug so labeled will remain safe and effective for the remaining non-patented methods of use.

In April 2008, Caraco amended its ANDA to replace its Paragraph IV certification with a Section viii statement. The latter sought to carve out from the RLD labeling any reference to the method of use covered by the '358 patent. FDA ultimately rejected Caraco's requested "carve out" on the basis of the "use code narrative" that Novo had submitted for inclusion in the Orange Book.[4] Novo's "use code narrative" for the '358 patent (as amended by Novo in 2009) included (per FDA's regulations) a description of its approved indication: "A method for improving glycemic control in adults with type 2 diabetes mellitus." In rejecting Caraco's "carve out" request, FDA declined to undertake its own analysis of the '358 patent. The United States later explained that Caraco "could not carve out the single approved indication that corresponded to [Novo's] new use code because that would leave [Caraco's] labeling without any approved indication, rendering its drug not safe and effective."

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[4] FDA's Orange Book lists the patent number and expiration date of every patent that claims a drug that is the subject of an approved NDA or that claims a method of using the drug. By regulation, FDA also requires the NDA holder to submit, for each listed method-of-use patent, a "use code narrative" of up to 240 characters; FDA describes the narrative as a "description of the approved indication or method of use" for the approved drug. Pet. App. 212.

U.S. Br. 12. FDA rejected Caraco's challenge to Novo's 2009 revision of the use code narrative. Caraco did not seek judicial review under the Administrative Procedure Act from that decision, nor did it seek APA review of the rejection of its Section viii "carve out" request.

Instead, Caraco in June 2009 filed a counterclaim in the Michigan patent infringement litigation. The counterclaim sought an order, under 21 U.S.C. § 355(j)(5)(C)(ii), requiring Novo to "correct" the use code information regarding the '358 patent that it had submitted to FDA for inclusion in the Orange Book. Rejecting Novo's assertion that § 355(j)(5)(C)(ii) did not authorize such a counterclaim, the district court granted summary judgment to Caraco on the counterclaim. Pet. App. 67a-72a. It ordered Novo to submit a new use code narrative stating that the '358 patent covered "the use of repaglinide in combination with metformin to lower blood glucose." *Id.* at 65a-66a.

The Federal Circuit reversed the grant of summary judgment and vacated the injunction requiring Novo to amend its use code narrative. *Id.* at 1a-18a. The court explained that the counterclaim provision was limited to situations in which the patent listed in the Orange Book claimed neither "the drug for which the application was approved" nor "an approved method of using the drug." *Id.* at 11a-12a. Because all parties agreed that the '358 patent did, in fact, claim "an approved method of using" repaglinide, the appeals court held that Congress had not authorized Caraco to file a counterclaim. *Id.* The court said that if Caraco seeks to expedite approval of its ANDA through a Section viii statement, "its real complaint should lie

with the FDA, not with Novo," noting that it was FDA that approved Novo's amended use code narrative and denied Caraco's Section viii "carve out." *Id.* at 14a.

The appeals court also stated that if a generic manufacturer seeks through litigation to contest an infringement claim, it should do so in connection with its defense of litigation filed by the pioneer manufacturer in response to a Paragraph IV certification:

> This court recognizes that a broad use code covering all uses of a pharmaceutical could require generic manufacturers to prove specifically that their use will not overlap with and infringe the patented use. This proof, under Hatch-Waxman procedures, will take the form of a Paragraph IV lawsuit. In that context, the generic may provide proof that their use will not cause infringement of the patented use. This court perceives that the Hatch-Waxman Act will thus ensure that a generic drug for non-patented purposes will not be used for patented purposes via a simple section viii certification. Instead, the generic manufacturer will need to alleviate the risk of infringement or induced infringement in a proceeding that fully tests for infringement and its implications, including potential health and safety risks.

Id.

The Federal Circuit also provided an alternative basis for reversing the district court's injunction: "the

counterclaim provision only authorizes suits to correct or delete an erroneous patent number or expiration date. The authorization does not extend to use code narratives." *Id.* at 15a-16a. The appeals court held that Caraco's counterclaim was improper because it sought to "correct or delete" Novo's use code narrative, not merely the patent number or expiration date. *Id.* WLF does not address this alternative holding.

SUMMARY OF ARGUMENT

Novo's brief spells out multiple reasons why Caraco is not entitled to an injunction requiring Novo to amend its use code narrative. WLF focuses this brief on one of those reasons: the counterclaim provision adopted by Congress in 2003 is unavailable when, as here, the patent listed in the Orange Book claims "an approved method of using the drug." 21 U.S.C. § 355(j)(5)(C)(ii). Caraco struggles mightily to avoid the plain meaning of the quoted language, but that meaning is fully supported by common sense, standard grammar, and by the overall purposes of the 2003 statute (the "2003 Amendments") that added the counterclaim provision to the Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 301 *et seq.*

The counterclaim provision is available to Caraco only if it can show that the '358 patent "does not claim either . . . the drug for which the application was approved . . . or an approved method of using the drug." 21 U.S.C. § 355(j)(5)(C)(ii)(I)(aa) and (bb). Caraco argues that this language means that it need only show that there is at least one "approved method of using" repaglinide that is *not* claimed by the '358 patent. The

utter implausibility of Caraco's interpretation is most readily apparent if one examines the structure of the counterclaim provision. Under that structure, two propositions ("Proposition A" and "Proposition B") are parallel to one another, and the generic company must demonstrate both in order to assert a counterclaim. As Caraco reads the statute, Proposition B should be interpreted to mean, "There exists at least one FDA-approved method of use that the patent-at-issue does not claim." But if that interpretation is ascribed to Proposition B, there is no interpretation that can be given to Proposition A that would maintain the parallel structure between the two propositions. Proposition A unquestionably requires a showing that the listed patent does *not* cover the RLD. There is no way to express that meaning in a manner that parallels the meaning ascribed to Proposition B by Caraco (*i.e.*, that requires the generic company to demonstrate existence instead of nonexistence). That lack of parallelism is eliminated if one adopts Novo's interpretation: the counterclaim provision requires a generic company to demonstrate that the patent at issue claims neither: (a) the underlying drug; nor (b) any approved method of using the drug.

The 2003 Amendments were adopted to correct a specific problem identified by Congress in connection with the Federal Circuit's 2001 *Mylan* decision: pioneer drug companies listing in the Orange Book patents that claimed neither the RLD nor a method of using the drug. By doing so, a pioneer company could delay approval of an ANDA by forcing a generic company to file a Paragraph IV certification; once the certification was filed, the pioneer company could then file a patent

infringement suit, thereby triggering the Hatch-Waxman Act's 30-month stay of approval of the ANDA. *Mylan* held that Congress had not authorized generic companies to file suit to force pioneer companies to remove improperly listed patents from the Orange Book. *Mylan*, 268 F.3d 1323. The 2003 Amendments were designed to correct the precise problem illustrated by *Mylan*. No party contests the Federal Circuit's conclusion that the 2003 Amendment, as interpreted by the court of appeals, fully accomplished that purpose. Pet. App. 13a. Indeed, the 2003 Amendments "used exact language from *Mylan* in the new counterclaim provision." *Id.* Accordingly, there is no reason to attribute to Congress a desire to correct the distinct set of "abuses" alleged by Caraco (the writing of overly broad use code narratives), particularly given that FDA did not direct manufacturers to begin writing use code narratives until several months *after* Congress adopted the 2003 Amendments.

There is no merit to Caraco's assertion that the Federal Circuit's decision leaves it without an effective remedy. As the Federal Circuit noted, a Paragraph IV lawsuit permits "efficient resolution" of all infringement/invalidity issues in an environment that "fully tests for infringement and its implications." *Id.* at 14a. One serious issue that arises in an suit involving method-of-use patents is "induced infringement." *Id.* If generic versions of repaglinide are approved while the '358 patent is still in force, there is a serious danger that doctors and medical insurers will infringe the patent by prescribing repaglinide for use in combination with metformin. Novo is entitled to seek to block approval of Caraco's ANDA to the extent that it can demonstrate

that if Caraco wins approval, it will induce others to infringe the '358 patent.

Moreover, the structure and the legislative history of the 2003 Amendments make clear that Congress sought to avoid upsetting the balance created by the Hatch-Waxman Act. It sought to ensure that the interests of both pioneer and generic drug companies were respected. In particular, it placed strict limits on the litigating rights of generic companies. Congress recognized that forcing patent holders to face too broad an array of legal challenges to their patents could seriously undermine the value of those patents. Any such diminishment in value has the potential to undermine continued advances in health care. Steps designed to ease the entry of generic drugs into the marketplace may lead to short-term price reductions for consumers, but – as Congress recognized – consumers are best served if a balance is maintained between short-term cost concerns and the longer-term need to encourage the level of research-and-development funding necessary to ensure continued medical advances.

ARGUMENT

I. CARACO'S CLAIM DOES NOT FALL WITHIN THE NARROW COUNTERCLAIM AUTHORIZED BY THE 2003 AMENDMENTS

The FDCA does not create a private right of action to enforce or restrain violations of its provisions and accompanying regulations. *Buckman Co. v.*

Plaintiffs' Legal Committee, 531 U.S. 341, 349 n.4 (2001). *See* 21 U.S.C. § 337(a) ("All such proceedings for the enforcement, or to restrain violations, of [the FDCA] shall be by and in the name of the United States."). Accordingly, the Federal Circuit held in *Mylan* that Congress has not authorized generic companies to sue to enforce the FDCA provision that prohibits pioneer drug companies from listing in the Orange Book a patent that claims neither the RLD (that is, the FDA-approved drug to which the proposed generic drug will be compared) nor a method of using the RLD. *Mylan*, 268 F.3d at 1330. The court dismissed for failure to state a cause of action a lawsuit filed by a generic company that objected to an Orange Book listing of a patent that covered a metabolite of the RLD rather than the RLD itself. *Id.* at 1332.

In response, some Members of Congress sought to overturn the result in *Mylan* by adopting legislation that would have created explicitly the private right of action that *Mylan* had rejected. *See* Respondents Br. 6-8, 44-45. That legislation failed following "a firestorm of criticism from Republican legislators" and a statement by President Bush that the it "would unnecessarily encourage litigation around the initial approval of new drugs and would complicate the process of filing and protecting patents on new drugs." *Id.* at 7-8. The result is that *Mylan* continues as an accurate statement of current federal law: a generic company does not possess a free-standing right of action against a pioneer drug company to correct allegedly improper Orange Book listings, even if the improper listing is interfering with the generic company's ability obtain approval of an ANDA.

Instead, Congress adopted the 2003 Amendments as a compromise between those who sought to overturn *Mylan* and those who sought to avoid increased litigation between pioneer and generic companies. In particular, the 2003 Amendments added the counterclaim provision at issue in this lawsuit; it provides in full:

> (ii) Counterclaim to infringement action.
>
> (I) In general. If an owner of the patent or the holder of the approved application under subsection (b) for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant [for an ANDA], the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) on the ground that the patent does not claim either –
>
> > (aa) the drug for which the application was application was approved; or
> >
> > (bb) an approved method of using the drug.
>
> (II) No independent cause of action. Subclause (I) does not authorize the assertion of a claim described in subclause (I) in any civil action or proceeding other than a counterclaim described in subclause (I).

21 U.S.C. § 355(j)(5)(C)(ii).

The parties dispute the meaning of the phrase, "does not claim . . . an approved method of using the drug." Caraco asserts that the phrase ought to be interpreted to mean, "There exists at least one FDA-approved method of use that the patent at issue does not claim." *See* Petitioners Br. 23. Petitioners assert that they meet the conditions for asserting the counterclaim, because they have demonstrated that there are *two* (out of three) FDA-approved methods of using repaglinide that are not claimed by the '358 patent: (1) repaglinide administered alone; or (2) repaglinide combined with TZDs. *Id.*

That interpretation of the phrase is not plausible. The most natural reading of the words in that phrase is that Congress intended to require a counterclaimant to demonstrate that the patent-at-issue does not claim any approved methods of using the drug. Caraco's interpretation inverts the order of the words as actually written. Had Congress really intended the meaning suggested by Caraco, it much more likely would have written the statute as paraphrased above, rather than (as it actually did) phrasing the language in the negative. Novo has cited to numerous grammatical sources that support their interpretation – that "not . . . an" means the same as "not even one." Respondents Br. 29. Caraco cites no contrary authority. There is no reason for ascribing to the disputed language anything other than its most natural meaning. *See United States v. LaBonte*, 520 U.S. 751, 757 (1997) ("[W]e assume that in drafting this legislation, Congress meant what it said.").

Moreover, the interpretation supported by Caraco

leads to a number of statutory anomalies. First, under Caraco's interpretation, the counterclaim would *always* be available whenever (as here) the patent holder is basing its infringement action on a method-of-use patent. Suppose, for example, that Novo held three method-of-use patents for repaglinide, one for each of the three FDA-approved methods of using repaglinide. Suppose further that Novo's lawsuit alleged that Caraco's ANDA infringed the method-of-use patent covering use of repaglinide in combination with TZDs. Under Caraco's interpretation of the counterclaim provision, Caraco would still be permitted to proceed with its counterclaim seeking to "correct or delete" the Orange Book listing for the TZDs method-of-use patent. That is so, because there would be two "approved method[s] of using" repaglinide that the TZDs patent "does not claim" – namely, use of repaglinide by itself and use of use of repaglinide in combination with metformin. Under Caraco's interpretation, the counterclaim to "correct or delete" the TZDs patent could proceed, even though the NDA holder owns separate method-of-use patents covering the FDA-approved uses not claimed by the TZDs patent. Given Congress's evident concern that strict limits be imposed on the scope of the right of action granted to generic drug companies to challenge Orange Book listings, it is highly improbable that Congress would have wanted to permit a counterclaim whenever the patent holder is basing its infringement action on a method-of-use patent and FDA has approved more than one method of using the RLD.

Second, Caraco's proposed interpretation is inconsistent with the parallel structure created by

subclauses (aa) and (bb). As structured, the counterclaim provision requires the generic company seeking to assert an Orange Book counterclaim to make two parallel showings. It must show that the listed patent "does not claim" either "(aa) the drug for which the application was approved" or "(bb) an approved method of using the drug." Under Novo's interpretation, the two showings remain in parallel – the counterclaimant must show that the patent-at-issue asserts neither of two sorts of claims: (1) a claim for the RLD itself; or (2) a claim for an FDA-approved method of using the RLD.

Under Caraco's interpretation, the parallelism between (aa) and (bb) is lost. Caraco interprets (bb) as conveying the following requirement: a showing that there *exists* "at least one FDA-approved method of use that the patent-at-issue does not claim." Once that interpretation of (bb) is adopted, there is no way to express the meaning of (aa) in a parallel manner. The requirement imposed by (aa) can only be expressed in terms of a negative showing: the counterclaimant must demonstrate that the listed patent does *not* assert a claim for the RLD. There is no way to express that required *negative* showing in a manner that parallels the *affirmative* showing required under the meaning ascribed to (bb) by Caraco (*i.e.*, in a manner that requires the generic company to demonstrate existence instead of nonexistence). Had Congress not intended the parallel structure posited by WLF, it would have been unlikely to structure the counterclaim provision such that both (aa) and (bb) are listed as items that the counterclaimant must demonstrate that the listed patent "does not claim." The absence of parallelism

created by Caraco's interpretation of the counterclaim provision is an additional reason to reject that interpretation.

Moreover, as the Federal Circuit noted, Congress adopted the "exact language from *Mylan*" in crafting the counterclaim provision, Pet. App. 13a – thereby suggesting that it intended to address the precise situation encountered in *Mylan* rather than to grant generic companies to raise broad challenges to any and all "abuses" they perceived in Orange Book listings. In *Mylan*, the pioneer company, on the eve of approval of an ANDA for a generic form of BuSpar®, listed in the Orange Book a new patent that supposedly was BuSpar-related. The generic manufacturer filed suit, claiming that the patent "did not claim BuSpar or an approved method of using BuSpar." 268 F.3d at 1331. The appeals court dismissed the suit, holding that regardless whether the listing was improper, federal law did not grant ANDA filers a private right of actions to challenge the improper listing of patents in the Orange Book. *Id.* Because the 2003 Amendment adopted language that mirrored the precise claim in raised in *Mylan*, the court below concluded that Congress intended to limit the counterclaim provision to *Mylan*-type case in which the counterclaiming alleges that the listed patent "did not claim [the RLD] or an approved method of using [the RLD]." Pet. App. 13a (quoting *Mylan*, 268 F.3d at 1331). The court explained:

> The 2003 amendment used exact language from *Mylan* in the new counterclaim provision. This choice of legislative language suggests that the 2003 Amendment sought to correct the specific

> issue raised in *Mylan*, i.e., to deter pioneer manufacturers from listing patents that were not related at all to the patented product or method. Thus, the language selected for this Amendment supports this court's interpretation that "an approved method" means "any approved method." A patent listing that covers one amongst several approved methods of using a formulation protects that patented method and thus bears a direct relation to the purpose of the Orange Book listings. This court does not detect a situation such as the one [that] occurred in *Mylan*.

Pet. App. 13a.

Moreover, it is anachronistic to suggest that when Congress adopted the 2003 Amendments in June 2003, it did so in order to allow ANDA applicants to file counterclaims challenging overly broad Orange Book use code narratives – allegedly written by pioneer drug companies in an effort to delay generic competition. Use code narratives did not even exist until 2002; and until August 2003, they were written exclusively by FDA itself, not by pioneer drug companies. *See* 68 Fed. Reg. at 36, 683.

Caraco relies for its interpretation of the counterclaim provision almost exclusively on Congress's use of the phrase "correct or delete." Caraco asserts that the word "correct" would be rendered superfluous if the counterclaim were interpreted as suggested by Novo. To the contrary, Novo has suggested scenarios under its interpretation, under which the courts could

be called upon to "correct" information included in the Orange Book (e.g., correction of an inaccurate patent number). Respondents Br. at 38. But even if the Court concludes that Novo's interpretation would render the word "correct" superfluous, that alone would not be sufficient grounds to adopt Caraco's fanciful interpretation of "does not claim . . . an approved method of using the drug." Adopting Caraco's interpretation would require distorting the language and legislative history of the entire counterclaim provision – a far less appealing interpretive solution than simply concluding that a single word in the statute is surplusage.

II. THE DECISION BELOW PROMOTES "EFFICIENT RESOLUTION" OF ALL INVALIDITY/INFRINGEMENT ISSUES BY STEERING THEM TOWARD PARAGRAPH IV LAWSUITS

There is no merit to Caraco's assertion that the Federal Circuit's decision leaves it without an effective remedy. To the contrary, to the extent that Caraco disputes Novo's infringement claims, it can assert its position in connection with its defense of a patent infringement action. To the extent that Caraco is unhappy with the manner in which FDA has administered the Orange Book (*e.g.*, FDA's decision to permit Novo to amend its use code narrative or to deny Caraco's requested Section viii "carve out"), it can seek judicial review of FDA's actions under the Administrative Procedure Act. There is no reason to expand the scope of the limited counterclaim created by the 2003 Amendments simply because Caraco is

concerned that approval of its ANDA might be delayed if it is required to seek relief by other means.[5]

Indeed, there are particularly strong reasons to require Caraco to proceed under existing avenues of relief rather than grant it an expanded counterclaim right. As the Federal Circuit noted, a Paragraph IV lawsuit permits "efficient resolution" of all infringement/invalidity issues in an environment that "fully tests for infringement and its implications." *Id.* at 14a. If generic versions of repaglinide are approved while the '358 patent is still in force, there is a serious danger that doctors and medical insurers will infringe the patent by prescribing repaglinide for use in combination with metformin. Novo is entitled to seek to block approval of Caraco's ANDA to the extent that it can demonstrate that if Caraco wins approval, it intends to induce others to infringe the '358 patent.

The issue of induced infringement is well illustrated by the Federal Circuit's recent decision in *Astrazeneca LP v. Apotex, Inc.*, 633 F.3d 1042 (Fed. Cir. 2010). In that case, a generic company obtained an ANDA for a generic version of a budesonide drug through use of a Section viii statement (which asserted that the company would not infringe existing method-of-use patents for administering a budesonide inhalation suspension to treat respiratory diseases). The Federal

---

[5] For example, a federal district court might ultimately determine that Caraco has not infringed, or induced infringement of, the '358 patent, except that the current labeling (*i.e.*, the labeling without a carve out) is infringing. If the district court went on to determine the terms of an acceptable carve out, it is difficult to believe that FDA would not abide by that determination.

Circuit ultimately upheld a preliminary injunction against the generic company, finding that the product labeling – while not specifically recommending that the product be used in an infringing manner – was likely to induce third parties to infringe the patent. After a lengthy evidentiary hearing, the district court determined (and the Federal Circuit affirmed) that the patent holder had presented sufficient evidence to establish that the generic company intended to induce others to infringe the method-of-use patent. 633 F.3d at 1059-61. Such induced infringement issues could never be resolved in connection with a counterclaim to correct allegedly improper use code narratives. Rather, disputes such as those between Novo and Caraco will likely require a detailed examination of Caraco's actions to determine whether it intends to seek profits by inducing others to breach of the '358 patent. Such an examination will require courts to look at more than just Caraco's proposed labeling. Accordingly, it makes little sense to stretch the meaning of the counterclaim provision in order to permit Caraco to sue Novo over the use code narrative, when doing so is highly unlikely to resolve all issues between the parties.

Permitting patent holders to be subject to multiple rounds of litigation lessens the value of patents and reduces the incentives to invest in new, life-saving pharmaceuticals. *See* Jenny Mamey, *A Myriad of Misunderstanding Standing: Decoding Judicial Review for Gene Patents*, 113 W.V. L. REV. 1033 (2011) ("These incentives and benefits will be diminished if the availability of patent challenges continues to increase because patent holders will not want the hassles and costs of litigation or risk of patent invalidation to

interfere with their investment.").

The structure and the legislative history of the 2003 Amendments make clear that Congress sought to avoid upsetting the balance created by the Hatch-Waxman Act. It sought to ensure that the interests of both pioneer and generic drug companies were respected. In particular, it placed strict limits on the litigating rights of generic companies. *See, e.g.*, 21 U.S.C. § 355(j)(5)(C)(ii)(II) (stating that Subclause (I) does *not* create an independent cause of action by ANDA applicants but rather only permits Subclause (I) claims to be raised as a counterclaim to an infringement suit filed by a patent holder in response to a Paragraph IV certification). Congress recognized that forcing patent holders to face too broad an array of legal challenges to their patents could seriously undermine the value of those patents. Any such diminishment in value has the potential to undermine continued advances in health care. Steps designed to ease the entry of generic drugs into the marketplace may lead to short-term price reductions for consumers, but – as Congress recognized – consumers are best served if a balance is maintained between short-term cost concerns and the longer-term need to encourage the level of research-and-development funding necessary ensure continued medical advances.

Indeed, evidence indicates that, at least partly as a result of decreased protections for patents, annual pharmaceutical research and development in this country decreased in constant dollars in recent years, from $47 billion in 2007 to $44 billion in 2010. Gardiner Harris, "Federal Research Center Will Help

Develop Medicines," *New York Times* (Jan. 23, 2011). As Prof. Richard Epstein has warned:

> The very uncertainty about the underlying choice [between short-term cost savings through use of generic drugs and long-term health benefits from increased research and development brought about by increased rewards to patent owners] is reason enough to be cautious about any fresh efforts to advantage the generic drugs at the expense of their branded rivals. And the ultimate irony may well be this: the next generation of generic drugs is the current generation of patented drugs. Let the spigot shut too tightly and both sides of the market could suffer.

Richard A. Epstein, *Branded Versus Generic Competition? A Kind Word for the Branded Drugs*, 3 HASTINGS SCI. & TECH. L.J. 459 (2011).

CONCLUSION

Amicus curiae Washington Legal Foundation requests that the Court affirm the the judgment below.

Respectfully submitted,

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Dated: October 24, 2011

AMICUS CURIAE BRIEF

RECORD
AND
BRIEFS

No. 10-844

In the Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD. AND SUN PHARMACEUTICAL INDUSTRIES, LTD., PETITIONERS

v.

NOVO NORDISK A/S AND NOVO NORDISK, INC., RESPONDENTS

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF REP. HENRY A. WAXMAN AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

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INTEREST OF *AMICUS CURIAE*[1]

Amicus Curiae Rep. Henry A. Waxman is a Member of Congress with an important interest in this case. Rep. Waxman is the Ranking Member of the House Energy and Commerce Committee, the House Committee with jurisdiction over matters relating to the Food and Drug Administration ("FDA") and generic drugs. Rep. Waxman has long championed increased consumer access to safe and effective, lower-cost generic drugs and has a strong interest in the proper judicial construction of the laws effectuating this legislative goal – in particular, the legislation known as the Hatch-Waxman Act ("Hatch-Waxman"), of which Rep. Waxman was a principal architect.[2]

This case presents a question of congressional intent – namely, the meaning of, and purpose behind, the counterclaim provisions added by Congress in 2003 to Hatch-Waxman. Rep. Waxman is particularly well-suited to address this issue and believes that the Federal Circuit's narrow interpretation of the counterclaim provisions conflicts with Congress' intent in enacting them – i.e., to strengthen the generic drug approval process against brand company abuses by providing generic companies with a judicial remedy for correcting

---

[1] The parties have consented to the filing of this brief. No party, counsel for a party, or person other than *amici* or their counsel authored this brief in whole or in part or made a monetary contribution to fund its preparation or submission.

[2] The formal name of Hatch-Waxman is the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984).

inaccurate patent information submitted by the brand to FDA. Indeed, the Federal Circuit's construction of the statute, far from strengthening the Hatch-Waxman system, eviscerates certain of its key aspects – in particular, the process for expedited FDA approval of generic drug applications for unpatented uses under the statute's "section viii" – and, if adopted by this Court, would enable brand companies to improperly delay generic competition for years, costing consumers and the health care system dearly.

STATEMENT

The counterclaim provisions are part of a comprehensive Hatch-Waxman framework aimed at "mak[ing] available more low cost generic drugs." H.R. Rep. No. 98-857, pt. 1, at 14 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2647. See also *In re Barr Labs., Inc.*, 930 F.2d 72, 76 (D.C. Cir. 1991) (goal of Hatch-Waxman is "to get generic drugs into the hands of patients at reasonable prices – fast.") Hatch-Waxman has been a great success. In 1984, when the statute was originally enacted, only 19 percent of the drugs prescribed in the United States were generic.[3] Today, that number stands at 70 percent.[4] Generic drugs typically cost 80-85% less than their brand name counterparts. Increased access to generic drugs has saved consumers billions

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[3] Congressional Budget Office, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry* viii (July 1998) ("CBO Report").

[4] Susan Okie, *Multinational Medicines-Ensuring Drug Quality in an Era of Global Manufacturing*, 361 New Eng. J. Med. 737, 738 (2009).

of dollars[5] and helped hold down national health care costs.

Critical to the Hatch-Waxman framework is the process established by the statute and implemented by FDA to identify and resolve patent issues between generic and brand drug manufacturers.

A company seeking FDA approval for a generic version of an approved brand drug (the "reference listed drug" or "RLD") must submit an Abbreviated New Drug Application ("ANDA") in which, among other things, it must account for each patent related to the RLD. 21 U.S.C. 355(j). Some patents do not claim the composition of the approved drug product, but rather a method of using the drug product (for example, to treat a particular medical condition or to be administered with a second drug). Hatch-Waxman provides two options for ANDA applicants seeking FDA approval in spite of any unexpired "method of use" patents claiming an approved use of an RLD.

First, if the ANDA applicant seeks approval for a patented use of the RLD, it must submit a "Paragraph IV" certification stating that the patent claiming the use is invalid, unenforceable, or uninfringed by the proposed generic product. 21 U.S.C. 355(j)(2)(A)(vii)(IV). Upon receiving the required notice of the certification from the ANDA applicant, the holder of the RLD may within 45 days bring patent litigation ("Paragraph IV litigation") against the generic. 21 U.S.C. 355(j)(5)(B)(iii).

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[5] CBO Report at viii.

Commencement of this litigation automatically stays FDA approval of the ANDA for 30 months. *Id.*

However, in cases where a brand company method of use patent does not cover all approved uses of the RLD, the ANDA applicant may instead seek immediate FDA approval for *unpatented* uses by submitting a "section viii" statement. 21 U.S.C. 355(j)(2)(A)(viii). While FDA generally cannot approve an ANDA unless the proposed generic label matches the RLD's label (21 U.S.C. 355(j)(2)(A)(v)), a section viii approval allows the generic to "carve out" labeling referring to the patented use(s) of the RLD and include only labeling for unpatented uses. 21 C.F.R. 314.94(a)(8)(iv). Thus, whereas Congress expected that a Paragraph IV filing would lead to patent litigation between the generic and the brand and would delay FDA approval of the generic ANDA for at least 30 months, it envisioned that a section viii statement, if approved, would allow a generic to obtain immediate approval of its ANDA for uses outside the scope of patent coverage. See *Purepac Pharm. Co. v. Thompson*, 354 F.3d 877, 880 (D.C. Cir. 2004) ("[A] section viii statement indicates that a patent poses no bar to approval of an ANDA because the applicant seeks to market the drug for a use other than the one encompassed by the patent.")

In order for an ANDA applicant to properly address brand company patents, it must of course know which patents cover the RLD. Under the Hatch-Waxman system, the burden of providing this information falls on the holder of the RLD, which must submit to FDA certain patent information that the agency publishes in its *Approved Drug Products with Therapeutic Equivalence Evaluations*, known as the "Orange Book."

The Hatch-Waxman statute itself requires that a brand company seeking FDA approval of a new drug include in its New Drug Application ("NDA") the patent number and the expiration date of any patent which claims the drug or a use of the drug, and that could reasonably form the basis of a patent infringement suit. 21 U.S.C. 355(b)(1).[6] In June 2003, FDA issued regulations requiring the holder of an approved NDA to submit to the Orange Book, under penalty of perjury, additional specific information for each method of use patent claiming the approved drug, including,

> (1) Whether the patent claims one or more approved methods of using the approved drug product and a description of each approved method of use or indication and related patent claim of the patent being submitted;
>
> (2) Identification of the specific section of the approved labeling for the drug product that corresponds to the method of use claimed by the patent submitted; and
>
> (3) The description of the patented method of use as required for publication.

21 C.F.R. 314.53(C)(2)(ii)(P). This information is known as a "use code."

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[6] If the relevant patent is issued after the submission of the NDA, the applicant must amend its application to include the required patent information. 21 U.S.C. 355(b)(1).

In the preamble to its 2003 regulations, FDA emphasized that requiring NDA holders to submit specific use codes was "essential" to the Agency's, and the ANDA applicant's, ability to identify unpatented uses for the RLD that could serve as the basis for an immediate section viii approval. *Applications for FDA Approval to Market A New Drug*, 68 Fed. Reg. 36676, 36685 (June 18, 2003). The Agency explained that

> requir[ing] the NDA applicant or holder to identify specifically the approved uses claimed by the method of use patent . . . would permit ANDA . . . applicants, and us, to assess whether the ANDA . . . applicant is seeking approval for a use the sponsor states is claimed in the listed patent, and thus determine whether the applicant must submit a patent certification or may submit a section viii statement . . . .

Id. at 36682. Previously, FDA had required only an unsworn certification from the NDA holder that its listed patents covered the approved method(s) of use for the RLD. But the agency realized that NDA holders were submitting "inappropriate patent information" that misleadingly described the scope of their method of use patents and "led to confusion and then to litigation over an ANDA applicant's obligation to submit either a paragraph IV certification . . . or a 'section viii' statement." *Ibid.* Hence, the use code requirement.

However, FDA does not review the substance of method of use patents (e.g., to determine if a particular listed patent in fact covers a claimed

method of use). Hatch-Waxman does not require FDA to review substantively patent information submitted by NDA holders, and FDA's longstanding position has been that it lacks the resources and patent expertise to do so, and that patent issues should be resolved by private litigants in the courts. As FDA's Chief Counsel explained to Congress,

> as we understand the statute, it requires us to publish patent information on approval of the NDA, thus making the agency's role ministerial, and courts have so held. I think that one of the signal features of Hatch-Waxman is that generic and innovator firms are supposed to resolve their disputes about patent listings and about patents in general in private litigation in the courts, where the expertise really resides with respect to patent questions.

Legislative and Regulatory Responses to the FTC Study on Barriers to Entry in the Pharmaceutical Marketplace: Hearing Before S. Comm. on the Judiciary, 108th Cong. 6-7 (2003) ("*Barriers to Entry Hearing*") (statement of Daniel Troy, FDA Chief Counsel). FDA adhered to this approach in the 2003 regulations, rejecting calls that it review the substance of the newly-required use codes and reemphasizing that "[t]he courts have the experience, expertise, and authority to address complex and important issues of patent law." 68 Fed. Reg. at 36683.

At the same time FDA was considering and eventually issuing its 2003 regulations, Congress

was considering legislation to address a wide range of Hatch-Waxman issues, including NDA holders' submission of misleading patent information for the Orange Book. Committees in both Houses of Congress (including the Subcommittee on Health of Rep. Waxman's House Energy and Commerce Committee) held hearings on Hatch-Waxman reform, in which FDA actively participated, presenting its views on proposed legislation and/or explaining the reasons for and content of its regulations, first as proposed and later as issued.[7] FDA made Congress aware of the agency's new requirements that NDA holders submit specific method of use information. E.g., *Barriers to Entry Hearing* at 7 (statement of D. Troy, FDA Chief Counsel) ("As I mentioned, we have tightened the requirements and increased the information required for drug patent submission and listings . . . The required submissions include patent information on . . . approved uses of the drug"). FDA also made clear its view that substantive issues relating to the patent listing requirements should be resolved in litigation between the brand and the generic, not by the agency. *Id.* at 6-7.

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[7] E.g., *Barriers to Entry Hearing*, at 5-8 (statement of D. Troy, FDA Chief Counsel); *Examining the Senate and House Versions of the "Greater Access to Affordable Pharmaceuticals Act": Hearing Before S. Comm. on the Judiciary*, 108th Cong. 7-10 (2003) ("*Greater Access Hearing*") (statement of D. Troy, FDA Chief Counsel); *Examining Issues Related to Competition in the Pharmaceutical Marketplace: A Review of the FTC Report, Generic Drug Entry Prior to Patent Expiration: Hr'g Before Health Subcomm. of the H. Comm. on Energy and Commerce*, 107th Cong. 27-29 (2002) (statement of Lester Crawford, FDA Acting Commissioner).

Against this backdrop, and with the "invaluable help" of FDA (*Greater Access Hearing* at 119 (statement of Sen. Schumer)), Congress enacted the counterclaim provisions at issue here (among other amendments to Hatch-Waxman) in late 2003, as part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003.[8] These provisions allow an ANDA applicant to file a counterclaim against the brand company RLD holder in patent litigation

> seeking an order requiring [the brand company] to correct or delete the patent information submitted by the holder under [21 U.S.C. 355(b) or (c)] on the ground that the patent does not claim either –
>
> (aa) the drug for which the application was approved; or
>
> (bb) an approved method of using the drug.

21 U.S.C. 355(j)(5)(C)(ii)(I). As described by their main legislative architect, the counterclaim provisions were intended to "enforce the patent listing requirements at the FDA by allowing a generic applicant, when it has been sued for patent infringement, to file a counterclaim to have the brand company delist the patent or correct the patent information in FDA's Orange Book." 149 Cong. Rec. 31,200 (2003) (statement of Sen. Schumer).

In this case, petitioner Caraco filed an ANDA for a generic version of the diabetes drug

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[8] Pub. L. 108-173, 117 Stat. 2452.

repaglinide, for which the RLD was the respondent Novo's approved brand product Prandin®. J.A. 100-19. Caraco initially filed a Paragraph IV certification relating to an Orange Book-listed Novo patent (the "'358 patent"), J.A. 124-36, which led Novo to bring an infringement suit against Caraco and to a 30-month stay of FDA approval of Caraco's ANDA. J.A. 137-43. Based on FDA's recommendation, Caraco then amended its ANDA to include a section viii statement with regard to the patent's method claim (Claim 4) on the grounds that according to Novo's use code (J.A. 97-99), the '358 patent claimed only the use of repaglinide in combination with another drug, metformin, and not either of the other two approved uses. J.A. 166-76. FDA indicated that Caraco's section viii request was appropriate. Pet. App. 8a. Approval of this request would have allowed Caraco to carve out from its generic labeling information on the patented combination use and to receive immediate approval for generic repaglinide's approved unpatented uses.

Subsequently, however, Novo amended its use code description to state that the patent claimed "[a] method for improving glycemic control in adults with type 2 diabetes" – a description broad enough to encompass both the combination use of repaglinide claimed by the '358 patent and the unpatented uses. J.A. 371. FDA could not tell from Novo's use code whether the '358 patent claimed a use for which Caraco was seeking approval. Thus, FDA determined that it could not grant the section viii request. Caraco then filed a counterclaim in the Paragraph IV case seeking an order requiring Novo to amend the use code for the '358 patent to again make clear that this patent claimed only use of

Prandin® in combination with Metformin. J.A. 342-68.

The district court denied Novo's motion to dismiss the counterclaim and granted summary judgment for Caraco, ordering Novo to amend its use code for the '358 patent. Pet. App. 65a-103a.[9] A divided panel of the Federal Circuit reversed. Pet. App. 1a-52a.[10] The court of appeals held that the statute did not permit a counterclaim if, as here, the method of use patent covered *any* approved use of the RLD, even if it failed to cover other approved uses. Pet. App. 11a-13a. The Federal Circuit also held that use codes were not "patent information submitted by the holder under [21 U.S.C. 355(b) or (c)]" and therefore could not be the subject of an order requiring the brand company to correct or delete such information. Pet. App. 14a-17a. The Federal Circuit also denied rehearing *en banc*, over the dissent of Judge Gajarsa, who was joined by Judge Dyk, the dissenter from the panel opinion. Pet. App. 53a-64a.[11]

SUMMARY OF THE ARGUMENT

This Court faces two issues of statutory construction regarding the Hatch-Waxman counterclaim provisions. The first concerns the meaning of the words, "on the ground that the

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[9] See *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 649 F. Supp. 2d 661 (E.D. Mich. 2009) and *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 656 F. Supp. 2d 729 (E.D. Mich. 2009).

[10] See *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 601 F.3d 1359 (Fed. Cir. 2010).

[11] See *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 615 F.3d 1374 (Fed. Cir. 2010)

patent does not claim . . . an approved method of using the drug," and whether they preclude counterclaims if, as here, an Orange Book-listed patent claims at least one approved use of the RLD. The second concerns whether the words "patent information submitted under . . . [21 U.S.C. 355(b) or (c)]" include information submitted pursuant to FDA regulations, or only information specifically identified in the statute. The Federal Circuit interpreted each of these passages to invalidate Caraco's counterclaim seeking an order forcing Novo to amend its overbroad use code.

The Federal Circuit's narrow construction of the counterclaim provisions is inconsistent with the statutory text and structure and cannot be squared with Congress' intent in enacting the counterclaim provisions – to enable private litigants to seek through the courts the correction of inaccurate patent information submitted by brand companies to FDA and thereby to strengthen, among other aspects of the Hatch-Waxman system, the section viii process. The section viii process is a key feature of the Hatch-Waxman generic approval framework, designed to enable ANDA applicants, in cases where an approved use of the RLD is not covered by a brand company patent, to obtain immediate FDA approval for that unpatented use and to circumvent costly, prolonged Paragraph IV litigation that would delay generic competition for years. FDA's 2003 use code requirements sought to bolster the section viii process against brand company efforts to claim overbroad coverage for their patents, and the counterclaim provisions enacted only six months later were expressly intended to afford ANDA applicants a means of correcting inaccurate

(including overbroad) Orange Book listings in the courts – the forum FDA and Congress agreed should address substantive patent issues. The Federal Circuit mistakenly concluded that Congress was only trying to overrule the decision in *Mylan Pharmaceuticals, Inc. v. Thompson*, 268 F.3d 1323 (Fed. Cir. 2001), and thus limited the counterclaim provision to the facts of that case, failing to recognize that Congress and FDA had much broader objectives in mind.

Under the Federal Circuit's reading of the counterclaim provisions, an NDA holder, through an overbroad use code, can block its generic competitors' access to the section viii immediate approval pathway, leaving generics with the sole recourse of costly, prolonged Paragraph IV litigation that delays generic entry, *even when the use for which the ANDA applicant seeks approval is not covered by a patent at all – the precise situation for which section viii is intended*. In these circumstances, moreover, the generic would be unable to prove non-infringement of the brand patent (because it would be unable to remove the patent information from its labeling) and, unless it could meet the high hurdle of showing that the patent was invalid or unenforceable, would be forced to delay marketing until expiration of the brand company patent – a patent that under the section viii process is completely irrelevant. Thus, the Federal Circuit's reading of the counterclaim provisions, far from strengthening the section viii process, effectively guts it. This is not the result that Congress intended.

ARGUMENT

I. The Federal Circuit's interpretation of "on the ground that the patent does not claim . . . an approved method of using the drug" is inconsistent with Congress' intent.

The Federal Circuit interpreted "on the ground that the patent does not claim . . . an approved method of using the drug" to preclude counterclaims unless the listed patent claimed no approved use of the RLD. Pet. App. 11a-13a. This reading is completely inconsistent with the text and context of the counterclaim provisions. Congress intended these provisions to cover the situation presented here in which Novo's patent did not cover all approved uses of the product and its overbroad use code improperly extended the scope of its valid patent protection.

1. The plain language of the statute states that a counterclaim may be asserted by a defendant in patent litigation if there is "an approved method of using the drug" that "the patent does not claim" – precisely the case here. Interpreting the statute to mean something different from what it says, the Federal Circuit read "*an* approved method of using the drug" (emphasis added) to mean *any* approved method of using the drug. Congress' decision not to use the word that would have unequivocally signaled the intent ascribed to it by the Federal Circuit shows that Congress intended a different meaning – especially given that the plain language of the statute conveys that different meaning.

Congress was mindful of the precise words it used when it enacted the counterclaim provisions.

In general, Congress "has a special duty to choose its words carefully when it is drafting technical and complex laws[.]" *St. Martin Evangelical Lutheran Church v. South Dakota*, 451 U.S. 772, 791 (1981) (Stevens, J., concurring) (citation omitted). And nowhere is this truer than in the Hatch-Waxman context. Senator Schumer aptly noted that as Congress attempted to close "loopholes" used by brand companies to exploit the Hatch-Waxman process to delay generic competition, "the devil is in the details . . . there is perhaps no other statute for which this phrasing is more true. Change an 'an' to a 'the' and you go from huge savings to huge costs." *Greater Access Hearing* at 119 (statement of Sen. Schumer). Thus, the counterclaim provisions were "extremely carefully crafted." *Ibid.*

Congress' decision to use "an" in the counterclaim provisions instead of "any" was not unconscious or neutral. It demonstrated Congress' clear, careful intent to allow a counterclaim where the Orange Book-listed patent did not claim a particular – "an" – approved use, not just when the patent failed to claim "any" approved use at all. If Congress had wanted the statute to have a narrow application and to preclude counterclaims when the NDA holder filed a use code that claimed both patented and unpatented uses, it knew exactly what word to use – "any." But it chose not to use that word here. See *Central Bank of Denver v. First Interstate Bank of Denver*, 511 U.S. 164, 176-77 (1994) ("If . . . Congress intended to impose aiding and abetting liability [in section 10(b) of the Securities Exchange Act of 1934], we presume it would have used the words 'aid' and 'abet' in the statutory text. But it did not.") (citations omitted).

2. Congress' use of "any" elsewhere in the counterclaim provisions confirms that Congress understood the meaning and effect of that word, but opted for a different, broader approach in setting forth the grounds on which a counterclaim could be brought. *Lopez v. Gonzalez*, 594 U.S. 47, 55 (2006) ("[W]here Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion.") (internal quotation marks omitted). 21 U.S.C. 355(j)(5)(C)(ii)(II) states that "[s]ubclause I [i.e., the counterclaim provision] does not authorize the assertion of a claim described in subclause (I) in *any* civil action or proceeding other than a counterclaim described in subclause (I)." (emphasis added). There, Congress used "any" to state absolutely that a claim based on the grounds set forth in the counterclaim provision could *never* be asserted except as a counterclaim under that provision. If Congress had meant to assert, in the same section, the similarly absolute proposition that a counterclaim could *never* be asserted if the Orange Book-listed patent claimed at least one approved use of the RLD, it would have used "any" in the counterclaim provisions as well. *Central Bank*, 511 U.S. at 176 ("Congress knew how to impose aiding and abetting liability when it chose to do so.") (citations omitted).

3. "[O]n the ground that the patent does not claim . . . an approved method of using the drug" also complements the wording of the section viii provisions, which indisputably apply when an Orange Book-listed patent fails to claim at least one approved use of the RLD. Specifically, section viii

applies when the listed patent is "a method of use patent which *does not claim a use for which the applicant is seeking approval under this subsection.*" 21 U.S.C. 355(j)(2)(A)(viii) (emphasis added). No one suggests that Congress intended a section viii approval to require that the NDA's holder's patent claim *no* approved method of use – merely that there be a single, particular approved use not claimed by the patent. If Congress had intended to limit counterclaims to cases in which the patent claimed no approved use, it would not have used language that complements the section viii language (compare "does not claim . . . an approved method of using the drug" to "does not claim a use for which the applicant is seeking approval.") See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 669, 673 (1990) (noting "complementary" Hatch-Waxman provisions and interpreting statutory language in light of "the structure of the Act . . . taken as a whole").

4. The Federal Circuit's limitation of counterclaims to situations where the listed patent claimed no approved use renders superfluous the statute's language allowing the counterclaimant to seek an order "correct[ing]" the submitted information. *Astoria Fed. Sav. & Loan Ass'n v. Solimino*, 501 U.S. 104, 112 (1991) ("[O]f course we construe statutes, where possible, so as to avoid rendering superfluous any parts thereof.") (citation omitted). The counterclaim language provides that a counterclaimant may seek an order "requiring the holder to correct *or* delete the patent information...." 21 U.S.C. 355(j)(5)(C)(ii)(I) (emphasis added). If the counterclaim provisions were only intended to cover instances where the patent claimed no approved use, Congress would only have needed to provide for an

order that the NDA holder delist the patent and "delete" the information relating to the patent from the Orange Book. For "correct" to have any meaning in the statute separate and independent from "delete," Congress would also had to have contemplated, and did contemplate, a situation like this one – when the patent covered at least one approved use, but did not cover other approved uses, and where the patent information therefore needed to be amended ("correct[ed]"), as opposed to deleted outright, to reflect only the patented use. A reading that restricts the counterclaim provisions to situations in which deletion of the information is the only appropriate remedy fails to give full effect to the language Congress carefully chose.

That Congress included "correct[ion]" or "delet[ion]" of patent information as alternative remedies under the counterclaim provisions disposes of the Federal Circuit's suggestion that these provisions were intended as a limited response to *Mylan Pharmaceuticals, Inc. v. Thompson*, 268 F.3d 1323 (Fed. Cir. 2001). In *Mylan*, the NDA holder submitted for listing in the Orange Book information on a patent that claimed no approved use of the RLD. The ANDA applicant sought to have the patent delisted, but the Federal Circuit held that it had no private right of action to contest the NDA holder's submission. 268 F.3d at 1332. The Federal Circuit in this case concluded that the counterclaim provisions legislatively overruled *Mylan* and should be limited to its facts – i.e., situations in which the patent claimed no approved product and did not belong in the Orange Book at all. Pet. App. 12a-13a. However, the statutory language allowing a counterclaimant to seek an order requiring the NDA

holder to "correct" *or* "delete" Orange Book information makes clear that Congress intended to address brand company patent listing activities to which the appropriate response was *either* "delet[ion]" of patent information, as the ANDA holder sought in *Mylan*, *or* "correct[ion]" of that information, as Caraco sought here. If Congress had only wanted to address the *Mylan* situation, it would not have needed to provide for "correct[ion]" of patent information.

Despite the Federal Circuit's reliance on *Mylan* to explain its view of Congress' intent, nothing in the legislative history suggests that the counterclaim provisions were a direct response to that decision, Moreover, the holding in *Mylan* was that Hatch-Waxman did not provide ANDA applicants with *any* new rights of action that it could assert against the brand. 268 F.3d at 1332. This holding applied no less to Caraco's claim here that the brand company improperly extended the scope of its patents by submitting a use code that purports to cover both patented and unpatented uses than to Mylan's claim that the NDA holder improperly listed a patent that covers no patented use at all. There is nothing in the legislative history to suggest that even if Congress' goal in enacting the counterclaim provisions was to overrule the *holding* in *Mylan*, it intended only to address the *fact situation* in *Mylan*.

5. The reading of the statute that makes the most sense given its text and structure is also the *only* reading of the statute that makes sense given the context in which, and purposes for which, Congress enacted the counterclaim provisions. *Deal v. United States*, 508 U.S. 129, 132 (1993) (noting the "fundamental principle of statutory construction

(and, indeed, of language itself) that the meaning of a word cannot be determined in isolation, but must be drawn from the context in which it is used.") (citations omitted).

As discussed, *supra*, at 7-9, Congress was clearly aware of, and legislated in the immediate wake of, the 2003 FDA regulations requiring NDA holders to submit specific information on each approved use claimed by the patent. FDA made crystal clear in its preamble to the regulations that a key objective of the new requirements was to enable the agency and ANDA applicants to determine whether there were unpatented uses for the RLD that could serve as the basis for a section viii approval. The agency emphasized that

> [t]he specific method-of-use claims are *essential* to our review because [section viii] allow[s] ANDA . . . applicants to file statements which assert that the method-of-use patent does not claim a use for which the applicant is seeking approval. . . . Thus, the claim-by-claim listing of method-of-use patents will permit ANDA . . . applicants to assess whether they are seeking approval for a use claimed in the listed patent, and thus determine whether to submit a patent certification or a section viii statement.

68 Fed. Reg. at 36682 (emphasis added). See also *id.* ("To effectively implement the certification and section viii provisions set out in the statute, we must have adequate information concerning method-of-use patents.").

Against this backdrop, and with FDA's "invaluable help" (*Greater Access Hearing* at 90 (statement of Sen. Schumer)) Congress enacted the counterclaim provisions to "enforce the patent listing requirements at the FDA." 149 Cong. Rec. 31,200 (2003) (floor statement of Sen. Schumer). See also *Barriers to Entry Hearing* at 90 (written statement of Sen. Schumer) (noting that the legislation "includes a strong enforcement mechanism . . . which will give teeth to the FDA's new listing provisions."). It is inconceivable that Congress manifested its intent to "give teeth to the FDA's new listing requirements" by disallowing a counterclaim where the NDA holder (1) failed to provide FDA with precisely the information that the agency's regulations required (i.e., specific information regarding methods of use claimed by the patents) and (2) used an overbroad use code to thwart the section viii process that the regulations were expressly designed to strengthen.

The Federal Circuit's reading is particularly unwarranted because it denies ANDA holders the judicial forum that Congress and FDA agreed was best equipped to address the patent listing issues implicated by the FDA regulations. FDA's longstanding view, with which Congress agreed, was that the agency lacked the expertise to substantively review patent information submitted by NDA applicants/holders and that disputes regarding the substance of that information (such as whether a particular patent claimed a particular approved use) should be resolved in litigation between private parties. The counterclaim provisions acknowledged and respected FDA's limited role in the patent review process and were designed to "go[] farther

than the rule is capable of in ensuring that consumers will see real savings from closing these loopholes." *Ibid.* See also 149 Cong. Rec. 15,516 (2003) (statement of Sen. Schumer) ("In fact, when the FDA actually talked about closing these loopholes, it was made clear that legislation would be needed to finish the job"). The Federal Circuit's reading of the counterclaim provisions thoroughly undermines Congress' intention to vest authority for the correction of misleading Orange Book listings in the courts.

Congress did not intend to ignore the problem of overbroad use codes and to focus only on the listing of patents that claim no approved use at all. There is no meaningful distinction in this context between the listing of a patent that claims no approved use of the RLD and the submission of a use code narrative that fails to distinguish between patented and unpatented uses. Both tactics involve the submission of misleading Orange Book information. Both manipulate the patent listing process to claim patent protection where none exists and to delay generic competition by leaving an ANDA applicant that is eligible for immediate approval with the sole (and, as discussed infra at 24-26, likely unhelpful) recourse of costly paragraph IV litigation that might delay generic competition for years. And both are addressed directly by FDA's requirement that the NDA holder "identify specifically," under penalty of perjury, "the approved uses claimed by the method of use patent." 68 Fed. Reg. at 36682.

Congress, too, sought to address both tactics by providing for a counterclaim through which ANDA applicants can seek to have their applications

restored to an immediate approval track. There is no evidence whatsoever and it would defy logic to suggest that in creating a judicial mechanism to enforce the FDA regulations, Congress sought or had any reason to address these two situations differently. Pet. App. 63a (Gajarsa, J., dissenting from denial of rehearing *en banc*) (noting that the majority's reading of the counterclaim provisions produces "an untenable and absurd result" that "contravenes the intent of Congress.") If, as this Court noted in *Arlington Cent. Sch. Dist. Bd. Of Educ. v. Murphy*, 548 U.S. 291, 296 (2006), the plain meaning rule of statutory construction does not apply "where the disposition required by the text is . . . absurd," it is certainly true that the Court should reject an "absurd" reading of the counterclaim provisions that is *not* supported by the statutory text or context.

Indeed, the Federal Circuit's reading of the counterclaim provisions, far from advancing FDA's and Congress' goal of increasing access to generic drugs, would eviscerate the section viii process that FDA's regulations and the counterclaim provisions were designed to protect. The section viii process provides for immediate approval of an ANDA when there is no issue of patent infringement, validity, or enforceability that needs to be addressed through the Paragraph IV litigation process (because the ANDA seeks approval for a use not covered by a patent). The Federal Circuit's decision, however, allows a brand company, through an overbroad use code, to deny the ANDA applicant access to that process. Under the Federal Circuit's reading, an ANDA holder otherwise entitled to immediate approval under section viii must instead look to the

Paragraph IV litigation process and challenge the listed patent on grounds of non-infringement, invalidity, and/or unenforceability – the very process that the section viii alternative was designed to avoid, and that Congress recognized would delay generic competition for years.

Even if the NDA holder is ultimately unsuccessful in the Paragraph IV litigation, the important point is that because of the automatic stay, it has been able to delay generic competition for at least 30 months while the litigation is ongoing. It is clear that generics "quickly gain a large share of the market" upon their approval by FDA. CBO Report at 28. The Congressional Budget Office found that for each of seven of the most prescribed drugs, generic companies gained 65% or more of the market within two years of entry. *Id.* Thus, it is a victory in and of itself for a brand company to lock a generic company into Paragraph IV litigation that will maintain the stay and delay the onset of generic competition, regardless of the eventual outcome of the litigation. That is what overbroad use codes, no less than the listing of a patent that claims no approved use, are designed to achieve,.

To make matters worse, moreover, as Judge Dyk's dissent, Judge Clevenger's concurrence, and Judge Gajarsa's dissent from the denial of rehearing *en banc* all recognized, an ANDA applicant that sought a section viii approval but was involuntarily forced into Paragraph IV litigation because of an overbroad use code would not be able to prove non-infringement because it would have no basis for distinguishing its label from the brand's. *See* Pet. App. 20a (Clevenger, J., concurring) (noting that as a result of the court's decision, "Caraco can no longer

assert that its proposed labeling does not infringe the '358 patent");[12] Pet. App. 50a (Dyk, J., dissenting) ("Novo's adoption of a broad use code for PRANDIN likely prevents Caraco from being able to disprove infringement in the paragraph IV lawsuit, because Caraco is now compelled to include information regarding the patented combination therapy in its label."); Pet. App. 63a (Gajarsa, J., dissenting from denial of rehearing *en banc*) ("Caraco . . . cannot disprove infringement . . . because the FDA requires it to use Novo's original label, which includes information regarding the patented combination therapy.")[13] Failure in the

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[12] Judge Clevenger determined that this result was FDA's fault because it had revised the labeling requirements for Prandin® and Novo's revision of its use code description was merely an effort to track the revised labeling. *Ibid.* But as Judge Dyk pointed out, the labeling changes in no way required Novo to change its original use code description, and the revised description clearly violated FDA regulations. Pet. App. 20a. The actual "fault" here lies in the assumption that the use code must track exactly the revised labeling even when it differs significantly from the scope of the listed patent.

[13] A Paragraph IV defendant may also prevail if it shows that the patent to which it certified was either invalid or unenforceable (for example, because the patentholder engaged in inequitable conduct before the U.S. Patent and Trademark Office). That is a high burden. *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1367 (Fed. Cir. 2011) (patents are presumed valid, and invalidity must be proven by clear and convincing evidence); *Therasense Inc. v. Becton Dickinson & Co.*, Nos. 2008-1511, -1512, -1513, -1514, -1595, 2011 WL 2028255 (Fed. Cir. May 25, 2011) (en banc) (inequitable conduct requires clear and convincing evidence of "but-for" materiality and specific intent to deceive).

Paragraph IV litigation would, in turn, delay the generic from going to market until the expiration of the patent that is the subject of the Paragraph IV litigation – *a patent that would be completely irrelevant if the generic company had been able to pursue a section viii carve-out.* Congress could not possibly have intended, and did not intend, the counterclaim provisions to have this effect.

II. The Federal Circuit's interpretation of "patent information submitted . . . under [21 U.S.C. 355(b) or (c)]" is inconsistent with Congress' intent.

The Federal Circuit also held Caraco's counterclaim invalid on the grounds that the information Caraco sought to correct – the use code for the '358 patent – was not "patent information submitted by the [NDA] holder . . . under [21 U.S.C. 355(b) or (c)]," and therefore could not be ordered by a court to be "correct[ed]" or "delete[d]" under the statute. Pet. App. 14a-17a. The court of appeals held that such "patent information" included only the patent number and expiration date required to be submitted for Orange Book publication by the statute itself, and did not include the use code and other information required to be submitted under FDA regulations. *Ibid.* This narrow reading of "patent information," like the federal circuit's narrow reading of "on the ground that the patent does not claim . . . an approved method of using the drug," is directly contrary to the text, structure, and context of the statute. Congress clearly intended "patent information submitted . . . under section [21 U.S.C. 355(b) or (c)]" to include the use codes required under FDA regulations.

1. The plain language of the statute leaves no room to suggest that use codes are not "patent information submitted . . . under [21 U.S.C. 355(b) or (c)]." A use code is clearly "information" about a "patent." And use code narratives are certainly "submitted . . . under [21 U.S.C. 355(b) or (c)]" because they are submitted pursuant to FDA regulations implementing the NDA approval and post-approval requirements set forth in those sections. *Greater Access Hearing*, *supra*, at 129 (written statement of D. Troy, FDA Chief Counsel) ("FDA has implemented the statutory patent listing provisions by informing interested parties of what patent information is to be submitted, who must submit the information, and when and where to submit the information."). In this context, therefore, "submitted . . . under [21 U.S.C. 355(b) or (c)]" naturally means "submitted as part of the NDA process 'subject to' or 'governed by' 21 U.S.C. 355(b) or (c)." See *Ardestani v. INS*, 502 U.S. 129, 135 (1991) (defining "under" in an analogous context to mean "subject to" or "governed by"). There is no question that the use codes fall within that definition.

If Congress had wanted to limit the counterclaim language to provide only for the correction or deletion of the "patent information" expressly required by statute, it instead could easily have referenced patent information "required by" or "referenced in" or "defined in" 21 U.S.C. 355(b) or (c). Again, Congress' choice of words in the Hatch-Waxman context has particular importance. *Supra*, at 15. Congress had at its disposal language that would have conveyed the narrow intent ascribed to it by the Federal Circuit. The fact that Congress chose

language that is naturally read not to have that narrowing effect shows that Congress did not intend that effect.

2. Congress did not draft the "patent information" language on a blank slate. The statutory language mirrors the verbiage used by FDA in its regulations and in discussing the regulation with Congress, to which the agency provided "invaluable help" (*Greater Access Hearing* at 119 (statement of Sen. Schumer)) in the process of drafting the statute. E.g., 21 C.F.R. 314.53 (entitled "*Submission* of *patent information*") (emphasis added); 21 C.F.R. 314.53(C)(2)(ii)(P) (requiring "*[i]nformation* on each method of use patent including the following[.]") (emphasis added); 68 Fed. Reg. at 36683 ("[W]e believe that it is necessary than an NDA holder *submit* more specific *information* on the approved methods of use protected by a submitted patent") (emphasis added); *Barriers to Entry Hearing* at 7 (testimony of D. Troy, FDA Chief Counsel) ("[W]e have tightened the requirements and increased the *information* required for drug patent *submission* and listings) (emphasis added).

FDA understood use codes to fall within the definition of "patent information submitted . . . under [21 U.S.C. 355(b) or (c)]," and Congress, in repeating FDA's language and working closely with the agency in drafting the counterclaim provisions, sought to ratify the agency's understanding. Pet. App. 37a (Dyk, J., dissenting) ("[I]t is well established that where, as here, Congress was specifically aware of the agency's interpretation of a statutory term at the time the statute was enacted, this is compelling evidence of legislative adoption of the agency's interpretation") (citing cases). At the

very least, Congress' decision to use the same language as FDA shows that its intent was to afford this language a broad scope: If Congress, in full awareness of the FDA's interpretation, had intended to adopt a different, more narrow interpretation than FDA's, it would not have used the same words FDA used. See *Whitman v. Am. Trucking Ass'ns, Inc.*, 531 U.S. 457, 468 (2001) ("Congress . . . does not alter the fundamental details of a regulatory scheme in vague terms or ancillary provisions – it does not . . . hide elephants in mouseholes.") (citations omitted).

3. The Federal Circuit suggested that because the original Hatch-Waxman statute contained an "express statutory definition" limiting "patent information" to the patent number and expiration date, this definition also applies to "patent information" as it appears in the counterclaim. Pet. App. 15a. The court of appeals' underlying premise, however, is incorrect. As Judge Dyk noted in his dissent, Hatch-Waxman does not define "patent information." Pet. App. 27a. And although the only patent information *required* to be submitted by Hatch-Waxman is the patent number and expiration date, the statute clearly envisions, and in fact cannot be implemented effectively without, specific information relating to patents and the particular methods of uses they cover.[14] Indeed, both the Paragraph IV and section viii provisions in Hatch-Waxman *depend on* the availability to ANDA

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[14] The Federal Circuit did not question FDA's authority to promulgate the use code regulations. Nor has Novo suggested at any point in this litigation that FDA lacked such authority.

applicants and FDA of information that will relate the brand company patents covering particular methods of use to the methods of use approved by FDA for the RLD's. Pet. App. 30a (Dyk, J., dissenting) (reviewing the statute and concluding that Hatch-Waxman "plainly contemplates that 'patent information' will include information that describes the scope of the patent and that relates the patent to the drug or method of use."). This information cannot be gleaned merely from a listing of a patent number and expiration date. FDA itself recognized that more specific information than what was required in the statute was "necessary" for it "[t]o effectively implement the [Paragraph IV] and section viii statement provisions." 68 Fed. Reg. at 36682-83. And the counterclaim provisions were Congress' way of enforcing these important requirements.

That Congress and FDA both recognized the need for the submission of patent information other than patent number and expiration date undermines the court of appeals' view that in enacting the counterclaim provisions, Congress was adhering to an earlier fixed and narrow "definition" of "patent information." Congress did not have such a limited perspective and fully expected that FDA needed to, and in fact would, develop additional patent listing requirements, as it did in 2003 when it enacted the use code regulations. There is no basis on which to distinguish between the "patent information" that Congress initially required in the statute and the "patent information" that Congress authorized and fully expected FDA to require in order to implement the statute effectively.

4. The Federal Circuit's reading of "patent information submitted . . . under [21 U.S.C. 355(b) or (c)]," like its reading of "an approved method of using the drug," is irreconcilable with Congress' clear intent to provide a judicial mechanism for the correction of inappropriate patent listings. The use codes that the Federal Circuit deemed to be outside the scope of the counterclaim provisions were the very information that FDA required in its regulations and that the agency deemed critical to its efforts to administer the section viii process that allows for expedited generic competition. In fact, without correct method of use information, FDA cannot determine whether ANDA applicants have filed appropriate section viii certifications to the method of use patent, as required by statute. As discussed, *supra*, at 7-9. Congress intended the counterclaim provisions to provide a means of correcting inaccurate Orange Book information in the forum that FDA and Congress had consistently agreed was best equipped to address patent listing issues – the courts. It makes no sense to suggest that Congress did not intend the counterclaim provisions to apply to patent information that FDA specifically required in the regulations – especially given that, as discussed *supra*, the submission of incorrect use codes claiming both approved and unapproved uses has the same purpose and effect as the improper listing of a patent that claims no approved use at all.

Again, the Federal Circuit's narrow reading of the counterclaim provisions would fatally undercut the section viii framework. If an ANDA applicant cannot file a counterclaim to require the NDA holder to amend overbroad use code narratives, there is

nothing to stop the manipulation of the patent listing process to prevent ANDA applicants and FDA from identifying unpatented uses that are suitable for expedited section viii treatment. That an ANDA applicant otherwise eligible for section viii treatment could still seek recourse through prolonged Paragraph IV litigation that the section viii process was intended to avoid and that the ANDA applicant has little chance of winning (*supra*, at 24-26) is cold comfort and plainly inconsistent with Congress' intent to provide ANDA holders with the choice of the Paragraph IV and section viii pathways.

CONCLUSION

The decision below should be reversed.

Respectfully submitted.

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